VOLUME 78 • SEPTEMBER 1957 • NUMBER 3

A.M.A. ARCHIVES OF NEUROLOGY & PSYCHIATRY

SECTION ON NEUROLOGY

Relationship of Blood Glucose to Changes in "Insulin Sensitivity" During Insulin Shock Therapy
Ivan F. Bennett, T. V. Letonoff, William Winick, and F. C. Dohan

Pineal Gland Displacement in Acute Cerebrovascular Occlusion
Jack B. Drori, Samuel Tartakoff, and Marjorie J. LeMay

Arteriographic Demonstration of the Collateral Circulation of the Cerebral Hemispheres
Lester A. Mount and Juan M. Taveras

Effects of Chlorpromazine on Cerebral Circulation and Electroencephalogram in Cats
David H. Ingvar and Ulf Soderberg

Experimentally Induced Epilepsy in the Cat with Injury of Cornu Ammonis
John D. Green, Carmine D. Clemente, and Jacob de Groot

Alterations in Mental Function and Paroxysmal Cerebral Activity
Kenneth A. Kooi and H. Birnet Hovey

Abstracts from Current Literature

SECTION ON PSYCHIATRY

Serum Copper and Oxidase Activity in Schizophrenic Patients
M. K. Horwitt, B. J. Meyer, A. C. Meyer, C. C. Harvey, and D. Haffron

Need for a New Subdiscipline in the Medical Profession
Lawrence S. Kubie

Reliability of Epinephrine-Methacholine (Mecholyl) Testing
R. Bruce Sloane, David J. Lewis, and Patrick Slater

Depressive and Paranoid Reactions
Charles E. Orbach and Irving Bieber

Adrenocortical Response and Phosphate Excretion in Schizophrenia
J. A. F. Stevenson, J. B. Derrick, G. E. Hobbs, and E. V. Metcalfe

Effects of Lysergic Acid Diethylamide (LSD) on the Time Sense of Normals
William K. Boardman, Sanford Goldstone, and William T. Lhamon

Book Reviews

AMERICAN MEDICAL ASSOCIATION PUBLICATION

COLONIAL HALL

One of Fourteen units in "Cottage Plan"

For Nervous Disorders

Maintaining the highest standards since 1884, the Milwaukee Sanitarium Foundation continues to stand for all that is best in the contemporary care and treatment of nervous disorders.

Photographs and particulars sent on request.

Josef A. Kindwall, M.D.
Carroll W. Osgood, M.D.
William T. Kradwell, M.D.
Benjamin A. Ruskin, M.D.
Lewis Danziger, M.D.
James A. Alston, M.D.
Edward C. Schmidt, M.D.
Isaac J. Sarfatty, M.D.

★

Waldo W. Buss, Executive Director

Chicago Office—1509 Marshall Field Annex Bldg.
25 East Washington St.—Wednesday, 1-3 P.M.
Phone—Central 6-1162

MILWAUKEE SANITARIUM FOUNDATION, INC.

Wauwatosa Wisconsin

TABLE OF CONTENTS

VOLUME 78 SEPTEMBER 1957 NUMBER 3

SECTION ON NEUROLOGY

ORIGINAL ARTICLES

PAGE

Relationship of Blood Glucose to Changes in "Insulin Sensitivity" During Insulin Shock Therapy
Ivan F. Bennett, M.D.; T. V. Letonoff, M.S.; William Winick, M.D., Coatesville, Pa., and F. C. Dohan, M.D., Philadelphia 221

Pineal Gland Displacement in Acute Cerebrovascular Occlusion
Jack B. Dreri, M.D.; Samuel Tartakoff, M.D., and Marjorie J. LeMay, M.D., Boston 228

Arteriographic Demonstration of the Collateral Circulation of the Cerebral Hemispheres
Lester A. Mount, M.D., and Juan M. Taveras, M.D., New York 235

Effects of Chlorpromazine on Cerebral Circulation and Electroencephalogram in Cats
David H. Ingvar, M.D., Lund, Sweden, and Ulf Soderberg, M.K., Stockholm 254

Experimentally Induced Epilepsy in the Cat with Injury of Cornu Ammonis
John D. Green, D.M. (Oxon.); Carmine D. Clemente, Ph.D., and Jacob de Groot, M.D., Los Angeles 259

Alterations in Mental Function and Paroxysmal Cerebral Activity
Kenneth A. Kooi, M.D., and H. Birnet Hovey, Ph.D., Salt Lake City ... 264

REGULAR DEPARTMENTS

Abstracts from Current Literature 272

SECTION ON PSYCHIATRY

ORIGINAL ARTICLES

Serum Copper and Oxidase Activity in Schizophrenic Patients
M. K. Horwitt, Ph.D.; B. J. Meyer, M.B., Ph.D.; A. C. Meyer, Ph.D.; C. C. Harvey, Ph.D., and D. Haffron, M.D., Elgin, Ill. 275

Need for a New Subdiscipline in the Medical Profession
Lawrence S. Kubie, M.D., New York 283

Reliability of Epinephrine-Methacholine (Mecholyl) Testing
R. Bruce Sloane, M.D., Montreal, Canada; David J. Lewis, M.D., Toronto, Canada, and Patrick Slater, M.A., London, England 294

Depressive and Paranoid Reactions
Charles E. Orbach, Ph.D., and Irving Bieber, M.D., New York 301

Adrenocortical Response and Phosphate Excretion in Schizophrenia
J. A. F. Stevenson, M.D.; J. B. Derrick, Ph.D.; G. E. Hobbs, M.D., and E. V. Metcalfe, M.D., London, Ont., Canada 312

Effects of Lysergic Acid Diethylamide (LSD) on the Time Sense of Normals
William K. Boardman, Ph.D.; Sanford Goldstone, Ph.D., and William T. Lhamon, M.D., Houston, Texas 321

REGULAR DEPARTMENTS

Book Reviews 325

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 78 SEPTEMBER 1957 NUMBER 3

COPYRIGHT, 1957, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

SECTION ON NEUROLOGY

HAROLD G. WOLFF, Chief Editor
525 East 68th Street, New York 21

BERNARD J. ALPERS, Philadelphia
CHARLES D. ARING, Cincinnati
PERCIVAL BAILEY, Chicago
STANLEY COBB, Cambridge, Mass.
DEREK E. DENNY-BROWN, Boston
ROLAND P. MACKAY, Chicago
HOUSTON MERRITT, New York
ADOLPH SAHS, Iowa City

SECTION ON PSYCHIATRY

ROY R. GRINKER Sr., Chief Editor
Institute for Psychosomatic and Psychiatric Research
29th Street and Ellis Avenue, Chicago 16

GEORGE E. GARDNER, Boston
M. RALPH KAUFMAN, New York
DOUGLASS W. ORR, Seattle
FREDERICK C. REDLICH, New Haven, Conn.
DAVID McK. RIOCH, Washington, D. C.
JOHN WHITEHORN, Baltimore

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $14.00. Canadian, $14.50. Foreign, $15.50. Price to students, interns, and residents, $8.00 in U. S. & possessions.

Single copies of this and previous calendar year, $1.50.

Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

12 ANSWERS TO THE QUESTION:

What do you have New in Psychiatry?

HYPNOGRAPHY: A Study in the Therapeutic Use of Hypnotic Painting. *By* **Ainslie Meares,** *Melbourne, Australia.* Describes a new technique in the treatment of nervous illness; throws new light on the highly dynamic nature of the hypnotic state and on the process of symbolism. Pub. '57, 324 pp., 385 il., Cloth, about $8.75

PSYCHIATRY IN THEORY AND PRACTICE. *By* **Beulah C. Bosselman,** *Univ. Illinois.* An overall orientation in the field. A suitable text for psychiatric residents and psychiatrists preparing for Board Examinations, because its presentation of therapy is authoritative, up-to-date, and complete. Pub. '57, 158 pp., Cloth, $4.00

CLINICAL APPLICATIONS OF SUGGESTION AND HYPNOSIS. (3rd Ed.) *By* **William T. Heron,** *Univ. Minnesota.* "Designed as a practical handbook with short chapters covering suggestion and suggestibility with general instructions in the professional use of hypnosis, including methods of induction, the depth of hypnosis, proper selection of patients, and precautions."—*GP.* Pub. '57, 184 pp., Cloth, $3.75

THE PSYCHOLOGIC STUDY OF MAN. *By* **John Money,** *The Johns Hopkins Univ.* Familiar knowledge in a new radical theoretical setting . . . takes an unorthodox point of view concerning motivation . . . shows the special significance of the concepts of information, sign decipherment and ego functioning. Pub. '57, 226 pp., 1 il., Cloth, $4.75

MENTAL HEALTH ADMINISTRATION. *By* **Jack R. Ewalt,** *Harvard Med. School.* It illustrates the problems by using detailed examples of how one goes about, for example, making budgets, staffing a hospital, determining food needs and assigning the roles of various professional groups in a program, etc. Pub. '56, 180 pp., Cloth, $5.50

CHILD PSYCHIATRY. (3rd Ed.) *By* **Leo Kanner,** *Johns Hopkins Univ.* "His greatest contribution lies in his sympathetic descriptions, and his lucid, common-sense delineation of the problems, both in maladjusted children and unhappy parents."—*J. Ment. Sc.* Pub. '57, about 788 pp. (6½ x 10), Cloth, $9.50

PRACTICAL PSYCHIATRY FOR INDUSTRIAL PHYSICIANS. *By* **W. Donald Ross,** *Univ. Cincinnati.* "The scope of the applications of psychiatric principles and methods in industrial medicine thus revealed comes as an exciting surprise."—From the Foreword by a leader in industrial medicine. Pub. '56, 404 pp., 2 charts, Cloth, $7.50

SIX CHILDREN. *By* **Estelle J. Foote.** A book for psychiatrists, pediatricians and general practitioners putting down clearly and in order, the diagnosis toward which each unusual characteristic of a child, or note in his history pointed. Also suggested treatment for each. Pub. '56, 332 pp., Cloth, $5.50

SPEECH CORRECTION AT HOME. *By* **Morris Val Jones,** *Golden Gate Coll., San Francisco, California.* FOR PRACTICAL USE: Each chapter deals with the speech problems which might confront any family. Besides giving directions for the care of the speech patient, the author summarizes briefly his convictions about aspects of SPEECH RE-EDUCATION. Pub. '56, 160 pp., 52 il., Cloth, $4.75

ALCOHOLISM. *Edited by* **George N. Thompson,** *Univ. Southern California.* Linked as it is to mental disease, the problem of alcoholism is discussed from every aspect, and the latest data available are discussed by well-known research workers and writers. Pub. '56, 560 pp., 89 il., Cloth, $9.50

THE MENTALLY ILL CHILD: A Guide for Parents. *By* **Steven B. Getz,** *California School for the Deaf, Berkeley,* and **Elizabeth Lodge Rees.** Explains to the parents the reasons for the many specialized examinations the child must have to determine his basic problem so that appropriate therapy may be started. Pub. '57, 100 pp., Cloth, $3.50

EMOTIONAL HAZARDS IN ANIMALS AND MAN. *By* **Howard S. Liddell,** *Cornell Univ.* The author's long continued investigations of conditioning and experimental neurosis in animals have led to the identification of certain emotional hazards common to animal and man. Pub. '56, 116 pp., (Amer. Lec. Objective Psychiatry), Lexide, $2.50

SEND FOR OUR

NEW 1957

CATALOG

OF 827 TITLES

CHARLES C THOMAS • PUBLISHER • SPRINGFIELD • ILLINOIS

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor. Articles are accepted for publication on condition that they are contributed solely to this journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length.

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

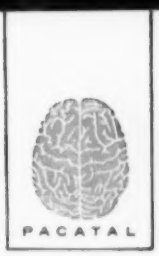
Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be limited to those used by the author in preparation of the article. They should be typed on a special page at the end of the manuscript. The citation should include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. References to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**



Only a short while ago withdrawn and angry at the world, now social and alert once more. Her schoolwork had dropped off alarmingly, she became morose, unkempt and shunned her fellow students. Because of these symptoms of mental disease or difficulties, Pacatal was instituted: 25 mg. t.i.d. Pacatal therapy saved this girl from a more serious breakdown.

"You wouldn't have recognized Nancy"

For patients on the brink of psychoses, Pacatal provides more than tranquilization. Pacatal has a "normalizing" action; i.e., patients think and respond emotionally in a more normal manner. To the self-absorbed patient, Pacatal restores the warmth of human fellowship . . . brings order and clarity to muddled thoughts . . . helps querulous older people return to the circle of family and friends.

Pacatal in contrast to certain phenothiazine compounds and other tranquilizers, does not "flatten" the patient. Rather, he remains alert and more responsive to your counselling. But, like all phenothiazines, Pacatal should not be used for the minor worries of everyday life.

Pacatal is well tolerated; its major benefits far outweigh occasional transitory reactions. Complete dosage instructions (available on request) should be consulted.

Supplied: 25 and 50 mg. tablets in bottles of 100 and 500. Also available in 2 cc. ampuls (25 mg./cc.) for parenteral use.

back from the brink with

Pacatal®

Brand of mepazine

WARNER-CHILCOTT

100 YEARS OF SERVICE TO THE MEDICAL PROFESSION

INDEX TO
NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA
Advertising in
A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an every-other month basis it would be necessary to consult the advertising section of a previous or *subsequent issue.*

ADAMS HOUSE ..... **Boston, Jamaica Plain, Mass.**
James Martin Woodall, M.D., Medical Director

APPALACHIAN HALL ..... **Asheville, N. C.**
Wm. Ray Griffin, M.D.

BALDPATE ..... **Georgetown, Mass.**
G. M. Schlomer, M.D.

BEVERLY FARM, INC. ..... **Godfrey, Ill.**
Dr. Groves B. Smith, Superintendent

DEVEREUX FOUNDATION ..... **Santa Barbara, Calif.—Devon, Pa.**
Helena T. Devereux, Director

FAIRVIEW SANITARIUM ..... **Chicago, Ill.**
Dr. J. Dennis Freund, Medical Director

HALL-BROOKE ..... **Greens Farms, Conn.**
Dr. Geo. S. Hughes, Medical Director

LIVERMORE SANITARIUM ..... **Livermore, Calif.**
O. B. Jensen, M.D., Superintendent and Medical Director

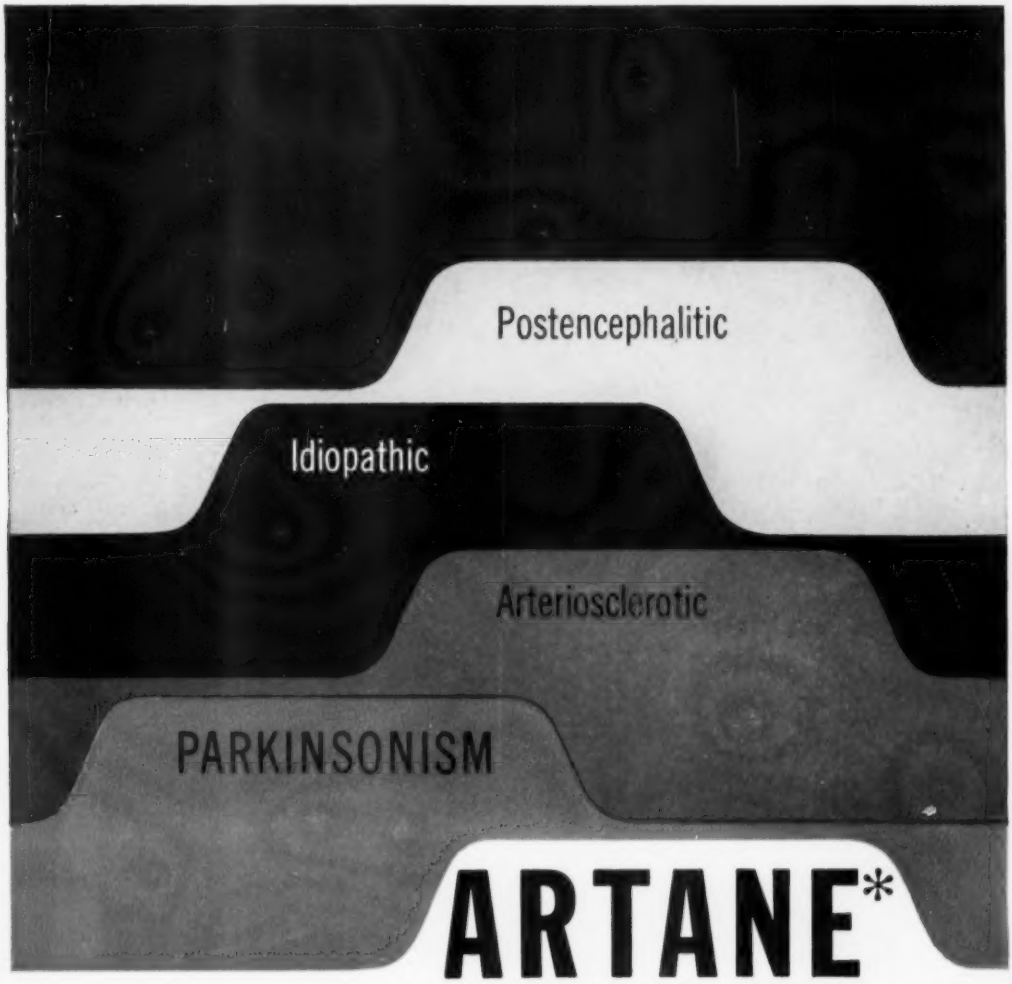
MENNINGER FOUNDATION ..... **Topeka, Kan.**
J. Cotter Hirschberg, M.D., Director

MILWAUKEE SANITARIUM FOUNDATION, INC. ..... **Wauwatosa, Wis.**

NORTH SHORE HEALTH RESORT ..... **Winnetka, Ill.**
Samuel Liebman, M.D., Medical Director

THE RING SANATORIUM ..... **Arlington, Mass.**
Benjamin Simon, M.D., Director

RIVER CREST SANITARIUM ..... **Astoria, Queensboro, N. Y. City**
and **BELLE MEAD FARM COLONY** ..... **Belle Mead, N. J.**
Dr. J. J. Kindred, Founder and Consultant



ARTANE*

HYDROCHLORIDE TRIHEXYPHENIDYL HCl LEDERLE

a first on the list

ARTANE is effective in all forms of Parkinsonism, in young and old, cardiac, hypertensive, postencephalitic and idiopathic types. Well tolerated, ARTANE maintains strong antispasmodic action over prolonged periods of treatment. ARTANE is remarkably free of serious toxic properties, has no deleterious effect on bone marrow function.

Supplied: 2 mg. and 5 mg. *tablets*, and *elixir* containing 2 mg. per teaspoonful (4 cc.)

Dosage: 1 mg. the first day, gradually increased, according to response, to 6 mg. to 10 mg. daily.

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

Lederle

*Reg. U. S. Pat. Off.

TO GET THROUGH TO THE PATIENT

SPARINE controls acute psychotic agitation without dulling mental acuity—thus inducing the calm accessibility so essential to psychotherapeutic rapport.

SPARINE is also highly effective in drug addiction and alcoholism for the control of withdrawal symptoms.

SPARINE is a well-tolerated and dependable agent when used according to directions. It may be administered intravenously, intramuscularly, or orally. Parenteral use offers (1) minimal injection pain; (2) no tissue necrosis at the injection site; (3) potency of 50 mg. per cc.; (4) no need for reconstitution before injection.

Professional literature available upon request.

Sparine*

Promazine Hydrochloride

HYDROCHLORIDE

10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride

*Trademark

Wyeth

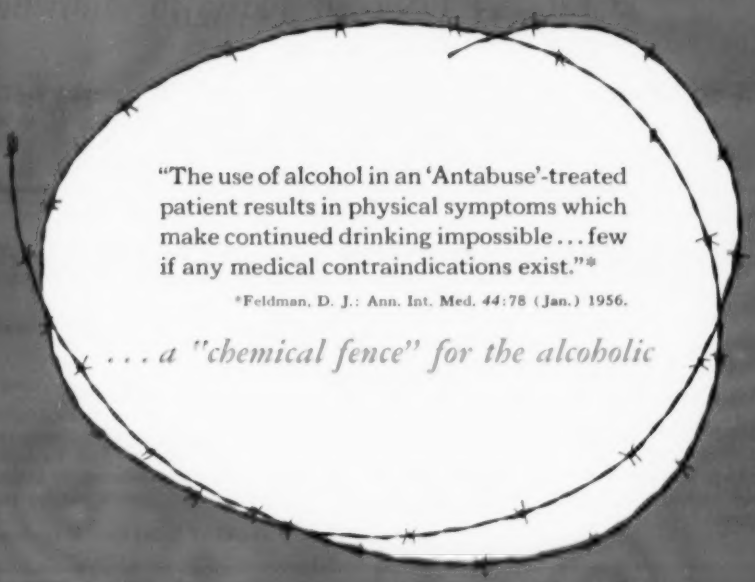
Philadelphia 1, Pa.

clinically proved in alcoholism

"ANTABUSE"®

brand of DISULFIRAM (tetraethylthiuram disulfide)

Feldman reports:
"... 'Antabuse' therapy constitutes a major advance in treatment."*



"The use of alcohol in an 'Antabuse'-treated patient results in physical symptoms which make continued drinking impossible ... few if any medical contraindications exist."*

*Feldman, D. J.: Ann. Int. Med. *44*:78 (Jan.) 1956.

... a "chemical fence" for the alcoholic

A brochure giving full details of therapy will be sent to physicians upon request.

"ANTABUSE" is supplied in 0.5 Gm. tablets (scored), bottles of 50 and 1,000.

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

8854

North Shore Health Resort

on the shores of Lake Michigan

WINNETKA, ILLINOIS

NERVOUS and MENTAL DISORDERS
ALCOHOLISM and DRUG ADDICTION

Modern Methods of Treatment

MODERATE RATES

Established 1901
Licensed by State of Illinois

Accredited by The Joint Commission on Accreditation of Hospitals

SAMUEL LIEBMAN, M.S., M.D.
Medical Director

225 Sheridan Road — Winnetka 6-0211

THE LIVERMORE SANITARIUM and PSYCHIATRIC CLINIC

Livermore, California
Telephone: Hilltop 7-3131
Oakland Office—411 30th Street

FOR THE TREATMENT OF NERVOUS AND MENTAL DISORDERS

THE OPEN CONVALESCENT DEPARTMENT, for nervous and general patients; the COTTAGE DEPARTMENT, for mental patients. Features: near Oakland and San Francisco; ideal climate; large beautiful grounds; hydrotherapy, athletic and occupational departments; clinical laboratory; large nursing force. Rates include room, suitable diet, medical care, general nursing and routine examinations.

HERBERT E. HARMS, M.D.—Superintendent

THE SOUTHARD SCHOOL

A residential school for elementary grade children with emotional and behavior problems.

THE CHILDREN'S CLINIC

Outpatient psychiatric and neurologic evaluation of infants and children to eighteen years.

Child Psychiatry Service

THE MENNINGER CLINIC

J. COTTER HIRSCHBERG, M.D., Director — Topeka, Kansas; Telephone 3-6494

in hospitalized psychotics

in agitated ambulatory psychoneurotics

new tranquilizer potency

in the full range of responsive mental disorders

Trilafon®

(pronounced Tril'-a-fon) perphenazine

Schering

potency increased 5 times over chlorpromazine[1]

relatively high therapeutic index[2]

jaundice—notably infrequent in studies to date[1]
significant hypotension—virtually absent[1-3]
skin rashes and nasal congestion—uncommon[1]
mild insomnia and motor restlessness—infrequent[1]

equally valuable in anxiety and tension states

For specific information regarding dosage, side effects, precautions and contraindications refer to Schering literature.

TRILAFON Tablets: 2, 4 and 8 mg., bottles of 50 and 500. 16 mg. (for hospital use), bottle of 500.

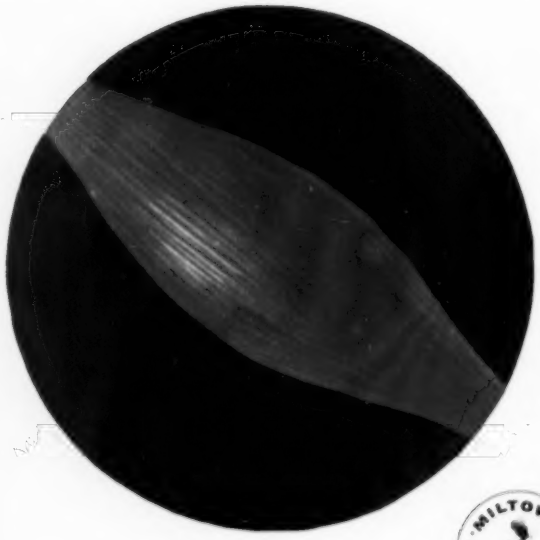
(1) Compilation of investigative studies, Schering Corporation. (2) Department of Pharmacology, Schering Corporation. (3) Ayd, F. J., Jr.: J. Am. Geriatrics Soc. 5:92, 1957.

outmoding older concepts

For anxiety, tension and muscle spasm in everyday practice.

- well suited for prolonged therapy
- well tolerated, relatively nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to phenothiazine compounds and rauwolfia derivatives
- orally effective within 30 minutes for a period of 6 hours

RELAXES BOTH MIND AND MUSCLE
WITHOUT IMPAIRING MENTAL OR PHYSICAL EFFICIENCY



Miltown®

tranquilizer with muscle-relaxant action

2-methyl-2-n-propyl-1,3-propanediol dicarbamate — U. S. Patent 2,724,720

Supplied: 400 mg. scored tablets
200 mg. sugar-coated tablets

Usual dosage: One or two 400 mg. tablets t.i.d.

Literature and samples available on request

WALLACE LABORATORIES, *New Brunswick, N. J.*

MILTOWN® THE ORIGINAL MEPROBAMATE® DISCOVERED AND INTRODUCED BY WALLACE LABORATORIES

CM-5108

SECTION ON
NEUROLOGY

Relationship of Blood Glucose to Changes in "Insulin Sensitivity" During Insulin Shock Therapy

IVAN F. BENNETT, M.D.; T. V. LETONOFF, M.S.; WILLIAM WINICK, M.D., Coatesville, Pa., and F. C. DOHAN, M.D., Philadelphia

The amount of insulin required to produce coma during the course of insulin shock therapy (IST) by the rapid induction method (Bond and Shurley[1]) is not constant but is considerably reduced after the first coma. We have previously observed (Dohan and associates[2]) that the mean lowest coma dose usually occurs in the fourth or fifth week of therapy and is approximately one-fourth or less of that required to produce the initial coma. Hypothetically, the most probable factors responsible for this change in "insulin sensitivity" might be (*a*) that a smaller dose of insulin causes an approximately equal or greater fall in true blood glucose or (*b*) that the central nervous system is "sensitized" with development of stupor or coma at greater blood glucose concentrations. This study was designed to test these possibilities.

We have published data[2] suggesting that repeated insulin shock is associated with decreased basal function of the anterior pituitary-adrenal system, thus reducing the effective concentration of insulin antagonists. The results described below indicate an enhancement of the blood-glucose-decreasing capacity of insulin, and thus support this hypothesis.

Received for publication June 17, 1957.

From the Veterans' Administration Hospital, Coatesville, Pa., and the Departments of Psychiatry and Medicine, University of Pennsylvania School of Medicine.

Dr. Bennett's present address is Chief, Psychiatric Research, Psychiatry and Neurology Service, Department of Medicine and Surgery, Veterans Administration, Washington 25, D. C.

Methods

Experimental Design.—True blood glucose concentrations were measured in three patients throughout the course of insulin shock therapy; one (PAR) with a constant dose of 400 units after the first three days, the other two (TRO and GOR) with the insulin dosage adjusted in the usual fashion of the Bond and Shurley technique.[1] The clinical state was recorded at 15-minute intervals (or less) in Subject PAR, but in Subjects TRO and GOR every half-hour (at the time of obtaining the blood specimen). An insulin reaction is defined as the appearance of stupor or coma. The symptoms and signs have been well described by Himwich.[3]

Glucose concentrations in venous blood were measured at 7:00, 7:30, 8:00, 8:30, 9:00, 9:30, and 10:00 a.m. Insulin was administered with hyaluronidase, by intramuscular injection, immediately after the 7:00 a.m. specimen was obtained. The reaction was terminated at 10:15 a.m. by the administration of carbohydrate, or sooner if clinical symptoms indicated (Dohan and associates[2]).

Chemical Studies.—All blood specimens for determination of true glucose were preserved with proper amounts of sodium fluoride and thymol. Protein-free blood filtrates were prepared by using powdered zinc hydroxide (Letonoff[4]). Analyses for blood glucose on the above filtrates agree closely with true glucose concentrations as measured by yeast fermentation. Recoveries at low concentrations of blood glucose were tested by using blood samples (taken after the injection of insulin) in which the measured glucose concentra-

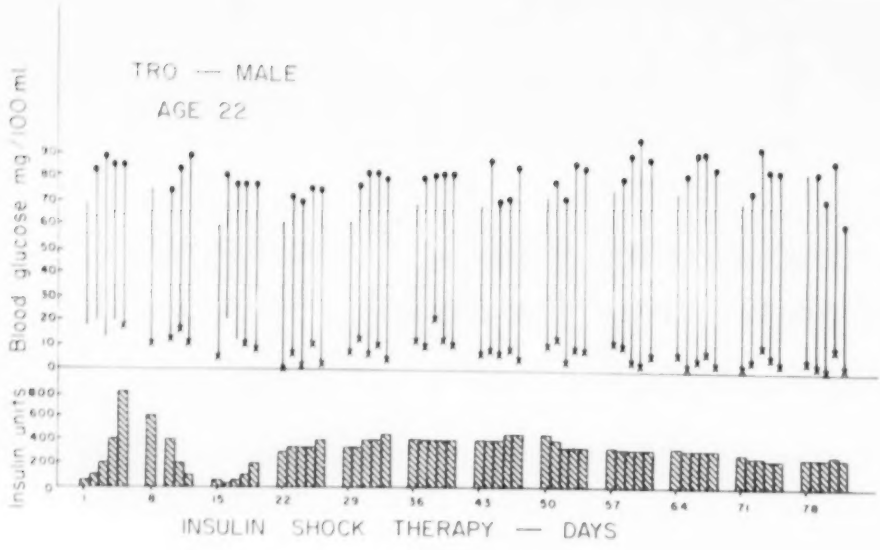


Figure 1

tions were less than 6 mg/100 ml. Glucose was then added in amounts equivalent to a concentration increase of 5 to 30 mg/100 ml. of blood. The error in recovery was equivalent to +0.5 mg/100 ml. of blood.

Results

Relationship of Blood Glucose at Initial and Subsequent Insulin Reaction.—Figures 1, 2, and 3 show the basal (7:00 a.m.) true blood glucose and either the blood glucose values in the first half-hour specimen taken after the appearance of an insulin reaction or, in the absence of insulin reaction, the lowest blood glucose value found in the half-hourly specimens from 7:00 to 10:00 a.m. inclusive. Out of a total of 105 reac-

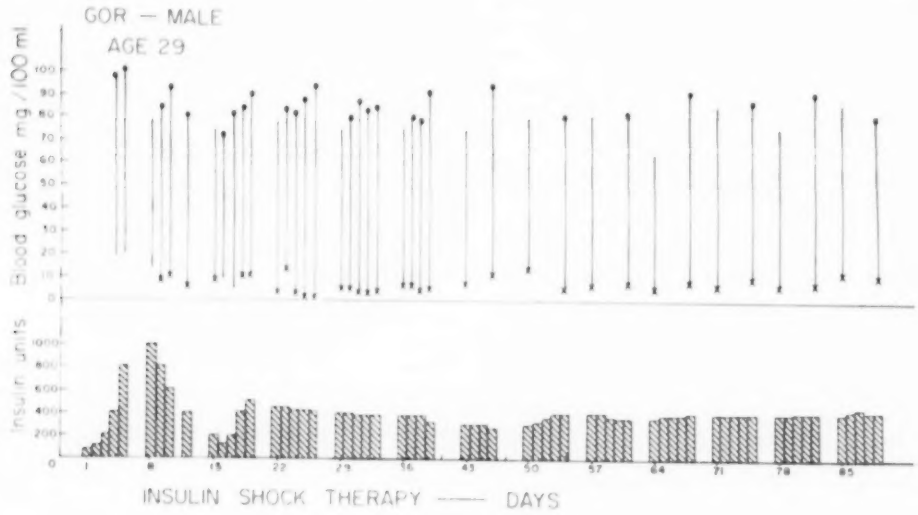


Figure 2

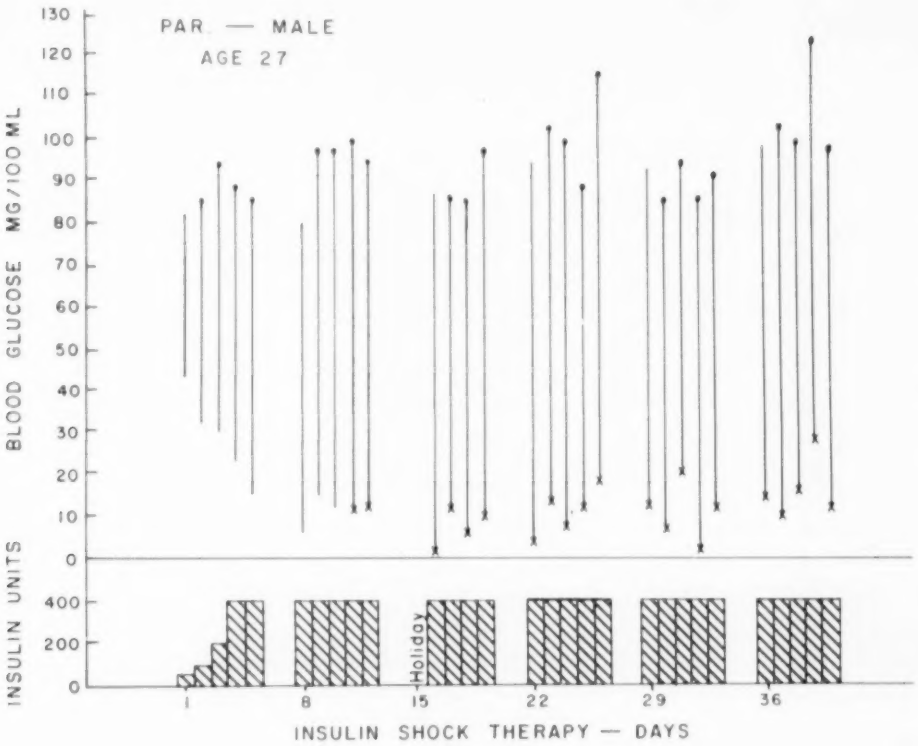


Figure 3

Figs. 1, 2, and 3.—Blood glucose concentrations during insulin shock therapy.

The symbol • indicates the glucose concentrations at 7:00 a.m., just prior to the injection of insulin, on therapy days other than Monday.

The Monday 7:00 a.m. values omit the • on the upper end of the lines.

The cross indicates the blood glucose concentration of the first blood sample (see "Methods") taken after the appearance of a reaction (coma or stupor).

The lines without a cross on the lower end indicate the lowest blood glucose value (taken at 30-minute intervals) on those days without a reaction.

These charts show that the blood glucose concentrations shortly after the appearance of a reaction were, in general, at the same level as or below that associated with the initial reaction. They also show that the preinsulin glucose concentrations were, in general, lower on Mondays than on other days.

tions (after the first), the onset of reaction was associated in only 14 instances with a glucose level higher than that at the time of the initial reaction (Table 1). In PAR the mean absolute fall was 84 mg. in those instances with reaction at levels of 12 mg. or less and was 87 mg. in those instances in which the blood glucose concentration was greater than 12 mg. This was due to the high basal (7:00 a.m.) values.

Rate of Fall of Glucose After Insulin.—Figures 4, 5 and 6 show the mean blood

TABLE 1.—*Blood Glucose Concentration at Onset of Coma or Stupor (Reaction)*

Subject	Initial Reaction	Number of Subsequent Blood Glucose Concentrations with Reaction	
	Mg/100 Ml.	≤Initial	>Initial
TRO	17	51	1
GRO	8	26	7
PAR*	12	14	6
Total		91	14

* See "Methods" regarding times of observation.

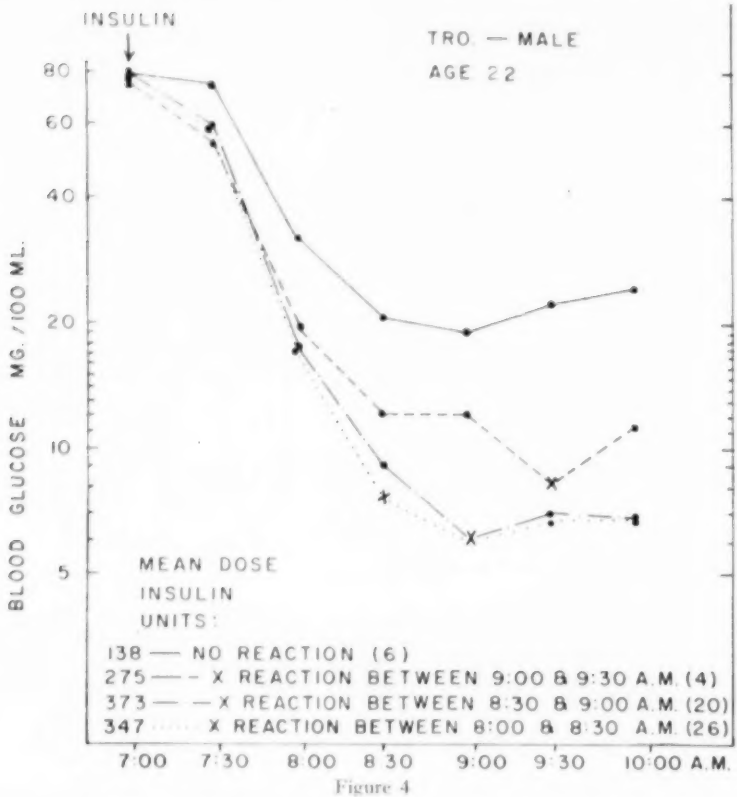


Figure 4

glucose values before and at half-hour intervals after the intramuscular injection of insulin. The mean concentration associated with the appearance of an insulin reaction varied slightly, but for the individual subject was lower than the mean lowest value found during those days during which a reaction did not appear. It will be noted that the rate of fall during the first one to one and one-half hours was approximately the same in those instances without a reaction as in those associated with a reaction. However, the concentration did not reach the low levels associated with a reaction.

Time of Reaction in Relation to Course of Insulin Shock Therapy.—In all three subjects there was a considerably higher proportion of early stupor or coma in the latter portion of the course of insulin shock therapy (Table 2). Inspection of Figures 1 and 2 shows that in Subjects TRO and GOR the differences in time of reaction were not due to the reactions occurring at a greater concentration in the second of the periods analyzed. In Subject PAR the reactions in the first three weeks occurred at a mean blood glucose value of 9 mg/100 ml. and in the second three weeks at a mean of 13.5 mg/100 ml. in both periods. This is to be compared with a mean fall of 75 mg/100 ml. on the five days the subject received 400 units without a reaction.

Basal Blood Glucose Concentrations During Insulin Shock Therapy.—Figures 1, 2, and 3 show the blood glucose concentration at 7:00 a.m. (basal) on Mondays to be appreciably below that of the 7:00 a.m. value on the preceding Friday in 25 of the 28 instances in which this comparison is possible. The basal glucose concentrations increased in Subject PAR[3] in the latter portion of the course of IST.

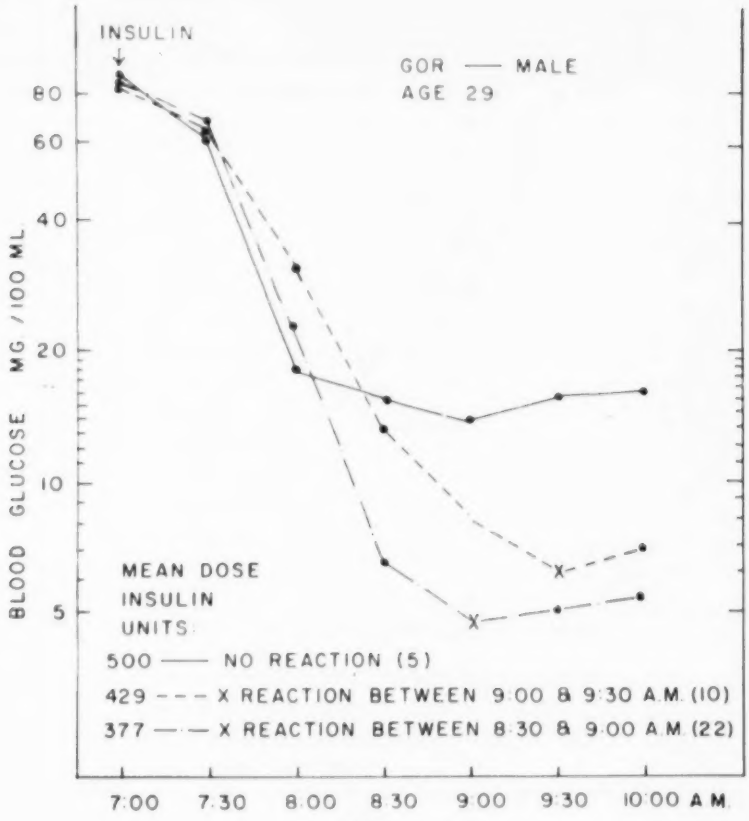


Figure 5

Comment

These observations clearly indicate that these three subjects did not show an "increased sensitivity" of the central nervous system to the concentration of blood glucose. In order to produce coma or stupor it was necessary that the blood glucose fall to levels approximately equal to that present at the initial reaction, even though the dose of insulin necessary to produce these levels decreased to 6% of the initial reaction dose (800 units) in Subject TRO and to 25% of the initial reaction dose (800 units) in Patient GOR. In Subject PAR the dosage was kept constant at 400 units per day. It seems evident, therefore, that the well-recognized change in insulin "sensitivity" during the course of insulin shock therapy is not related to a change in sensitivity of the central nervous system, but is due to changes in the response of the blood glucose to insulin. Only a few published studies (Kety and associates,[5] Forbes and Czarski,[6] Blumberg and associates[7]) deal with the concentration of "true blood glucose" during insulin coma or stupor during insulin shock therapy. The reported values are similar to those found by us. Evidence previously presented[2] showing a rise in the basal (7:00 a.m.) eosinophil counts and a fall in two of three instances in the basal plasma concentration of 17-hydroxycorticoids suggests that this change may be due to a decreased production of contrainsulin hormones. The contrainsulin factors probably include the growth hormone and the

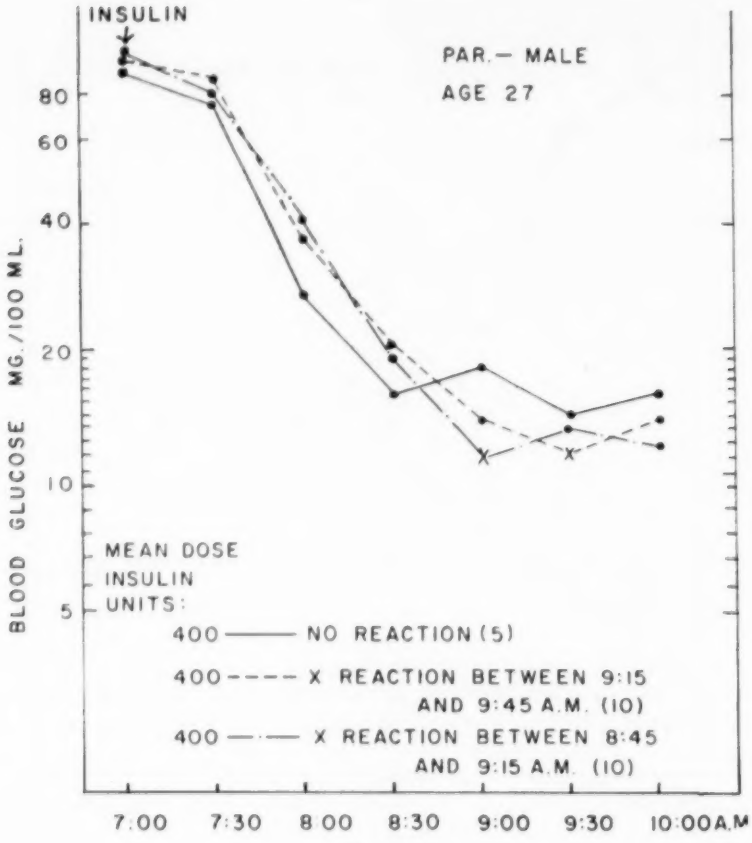


Figure 6

Figs. 4, 5, and 6.—Mean blood glucose concentration and insulin reaction (stupor or coma). The blood glucose concentrations are plotted on a logarithmic scale.

adrenal cortical glucogenic corticoids, epinephrine and the "pancreatic alpha-cell hormone" (Wolstenholme[8]). Recent experiments using rabbits also indicate a marked increase in insulin "sensitivity" with repeated insulin shock (Näätänen[9]). The reason for the lower basal (7:00 a.m.) blood glucose concentration value on Monday morning is not clear. However, it is possible that the large doses of insulin, extra food, and carbohydrate drinks from Monday through Friday are associated with a higher liver glycogen reserve, so that higher basal blood glucose concentrations may be maintained. Since no insulin or extra foodstuff was given on Saturday or Sunday, the liver glycogen reserve is probably lower and therefore associated with a lower value of blood glucose. We know of no clinical investigation to support this hypothesis.

TABLE 2.—*Time of Onset of Reaction During Course of Insulin Shock Therapy*

	TRO		PAR*		GOR†	
	Before 8:30 a.m.	After 8:30 a.m.	Before 9:15 a.m.	After 9:15 a.m.	Before 9:00 a.m.	After 9:00 a.m.
Course						
First half	7	16	1	6	1	5
Second half‡	20	10	9	5	13	1

* See "Methods" regarding time of observation.
† For GOR the first three weeks are compared with the second three weeks.
The last seven weeks also showed a high preponderance of early reactions.
‡ The duration of therapy for TRO was 12 weeks, and for PAR, 6 weeks.

Summary

"True blood glucose" concentrations were determined in three schizophrenic men throughout the course of insulin shock therapy (IST) given by the rapid induction method. The glucose concentrations associated with an insulin reaction (coma or stupor) were equal to or less than the value at the time of the initial reaction in 91 of 105 observations. In general, the reactions occurred sooner after insulin injection in the latter portion of the course of IST. The results indicate that the characteristic decrease in insulin dose required to produce a reaction during IST (increase in "insulin sensitivity") is due to an equal or greater fall in blood glucose with smaller doses of insulin. These results, with evidence previously presented, suggest that recurrent stimulation of the various endocrine organs producing contrainsulin hormones may result in a somewhat decreased basal production of these factors.

Dorothy Neudorff, R.N., and Gabriella Kennedy, R.N., obtained the blood specimens, and Doris Joslin and Mary Garton helped in preparation of the manuscript.

Veterans' Administration, Washington (25) D. C.

REFERENCES

1. Bond, E. D., and Shurley, J. T.: Insulin Therapy and Its Future, Am. J. Psychiat. 103:338 (Nov.) 1946.

2. Dohan, F. C.; Winick, W.; Purcell, M.; Bennett, I. F., and Hecker, A. O.: Response of Blood Eosinophiles and Plasma 17-Hydroxycorticoids to Insulin Shock Therapy, A. M. A. Arch. Neurol. & Psychiat. 73:47 (Jan.) 1955.

3. Himwich, H. E.: Brain Metabolism and Cerebral Disorders, Baltimore, Williams & Wilkins Company, 1951.

4. Letonoff, T. V.: A Zinc Hydroxide Powder for the Preparation of Protein-Free Filtrates of Blood, J. Biol. Chem. 106:693 (Sept.) 1934.

5. Kety, S. S.; Woodford, R. B.; Harmel, M. H.; Freyhan, F. A.; Appel, K. E., and Schmidt, C. F.: Cerebral Blood Flow and Metabolism in Schizophrenia, Am. J. Psychiat. 104:765 (June) 1948.

6. Forbes, W. H., and Czarski, T.: A Note on the Level of Glucose and of Nonfermentable Reducing Substances in Therapeutic Insulin Shock, J. Lab. & Clin. Med. 25:679 (April) 1940.

7. Blumberg, A. G.; Cohen, L.; Croghan, J., and Kelsey, D.: Apparent and True Blood Sugar Levels in Insulin Coma Therapy, J. Hillside Hosp. 5:41 (Jan.) 1956.

8. Wolstenholme, G. E. W., and Freeman, J. S., Editors: Hormonal Factors in Carbohydrate Metabolism, Ciba Foundation Colloquia on Endocrinology, Vol. 6, Boston, Little, Brown & Company, 1953.

9. Näätänen, E. K.: The Paradoxical Effect of Giant Intravenous Insulin Doses on Rabbits, Ann. med. exper. et biol. fennial. 32:186, 1954.

Pineal Gland Displacement in Acute Cerebrovascular Occlusion

Report of a Case

JACK B. DRORI, M.D.; SAMUEL TARTAKOFF, M.D., and MARJORIE J. LeMAY, M.D., Boston

Cerebral edema is generally assumed to be present in association with cerebral infarction, but it is not widely recognized that the edema can be of sufficient magnitude to cause a contralateral shift of the pineal gland or the ventricular system. Most of the standard textbooks of neurology [1-10] and of roentgenology [11-16] do not mention this phenomenon. Murphy,[17] in his textbook "Cerebrovascular Disease," has one reproduction of a film showing lateral displacement of the pineal gland to the right following thrombosis of the left internal carotid artery. He states briefly that in acute major infarction the pineal gland, if visible, may be displaced laterally and that air studies may simulate those of a brain tumor.

Recently we had the opportunity to study a case of cerebrovascular thrombosis in which the pineal gland was shifted to the contralateral side and then reverted to its midline position.

Received for publication Aug. 18, 1956.

From the Veterans' Administration Hospital, Boston; Tufts University Medical School, Department of Neurology, and Boston University School of Medicine, Department of Roentgenology.

Resident in Neurology, Psychiatry and Neurology Service, Veterans' Administration Hospital, Boston (Dr. Drori). Assistant Chief, Psychiatry and Neurology Service, and Chief, Aphasia Section, Veterans' Administration Hospital; Assistant Clinical Professor of Neurology, Tufts University Medical School (Dr. Tartakoff). Chief, Diagnostic Service, Department of Roentgenology, Veterans' Administration Hospital; Assistant Clinical Professor of Radiology, Boston University School of Medicine (Dr. LeMay).

Presentation of Case *

A 57-year-old white man, an insurance agent, was admitted to the Veterans' Administration Hospital, Boston, on Sept. 30, 1955, three hours after the sudden onset of right-sided numbness, followed by the development of weakness on the same side over a period of two hours. He did not lose consciousness and his speech was unaffected.

In 1951 he was found to have essential hypertension of 150-200/100-160, with normal renal functions. He had not had any head injury.

Physical examination revealed that he was well developed and well nourished, with T 98.6 F, P 84, and B. P. 240/160.

He was somewhat confused but oriented for time and place. He had a severe predilection type of weakness in the right arm and leg, more marked distally and associated with spasticity, hyperreflexia, and a positive Babinski sign. Right hemihypalgesia was present.

The fundi showed wiring of the arterioles with some AV nicking. There were no hemorrhages, exudates, or papilledema. A right homonymous hemianopsia was demonstrated. The pupils were equal and reacted well to light and in convergence. The corneal reflexes were intact. There was right central facial weakness. The remainder of the cranial nerves were normal.

The patient was right-handed, and his speech was normal.

Serology, white cell count, differential count, and Hgb were normal; urine gave a 3+ reaction for albumin.

On the evening of admission lumbar puncture revealed clear cerebrospinal fluid under pressure of 160 mm. of water, which contained 6 lymphocytes per cubic millimeter and a total protein of 27 mg. per 100 cc. Serology and colloidal gold curve were negative.

An EEG demonstrated a slow-wave focus in the left central region.

On the morning following admission he demonstrated a receptive aphasia, which three days later

* Courtesy of Robert M. Donaldson Jr., M.D.

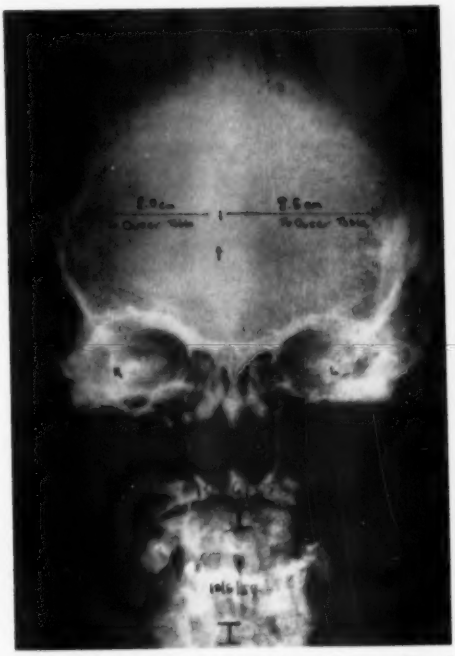


Fig. 1.—Skull film on sixth day of illness. Pineal gland shifted 5 mm. to contralateral side.

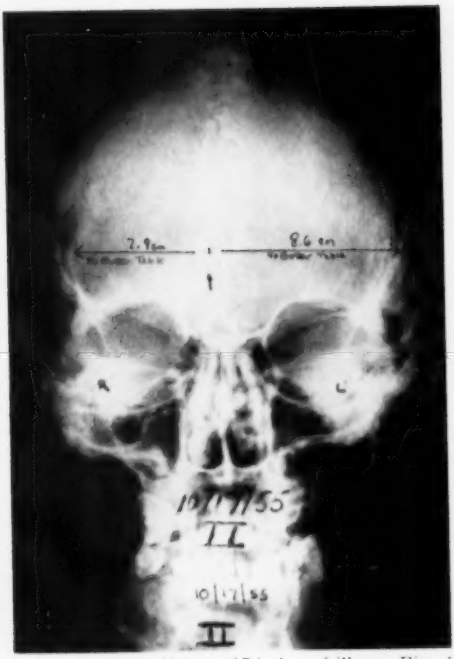
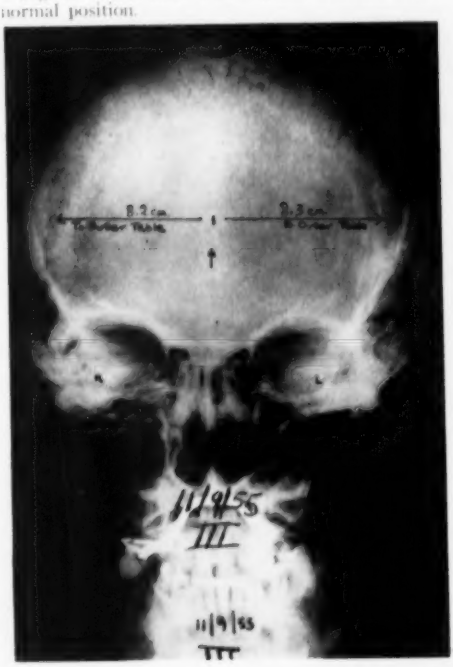


Fig. 2.—Skull films on 17th day of illness. Pineal gland shifted 7 mm. to contralateral side.

Fig. 3.—Skull film. Pineal gland reverted to its normal position.



had largely cleared. During the next month the strength in his right hand and arm gradually returned to a remarkable degree, but the weakness in the right leg, though less severe, persisted.

In spite of various and adequate trials on hypotensive agents, his blood pressure remained at 200-250/100-150. He was not in congestive or renal failure.

In the hospital he, for the first time, had two convulsions. They began with clonic movements in the right foot and spread to the right arm, becoming generalized and associated with cyanosis and loss of consciousness. His seizures were controlled with anticonvulsants. Repeat spinal fluid studies were unremarkable.

Serial EEG's showed a remarkable change. One month after his admission, coincidental with his clinical improvement, the record was only "minimally abnormal," with only a small vestige of a slow-wave disturbance in the left central-parietal region.

Skull films taken on the 6th hospital day showed the pineal gland to be displaced 5 mm. (Fig. 1), and on the 17th day 7 mm. (Fig. 2), to the right of the midline. On his 32d hospital day repeat films showed the pineal gland to be in its normal midline position (Fig. 3). This was confirmed one month later.

Fig. 4.—Pneumoencephalogram, lateral view. Left lateral horn dilated. Note localized dilatation posteriorly.

Treatment was begun with anticonvulsive and hypotensive medication, and he was discharged much improved, on Dec. 19, 1955.

On March 2, 1956, he had a seizure similar to the ones described previously, and he was rehospitalized. At this time he had a right hemihyperesthesia and occasional word-finding difficulty with slight dyscalculia, but no visual field cut. Otherwise he was much the same as on his discharge from the hospital. Subsequently his speech again improved. Because of the persistent focal motor and grand mal seizures, pneumoencephalography (65 cc. of air) was performed. Besides the generalized enlargement of the lateral ventricles (Fig. 4), there was marked localized enlargement of the left lateral ventricle posteriorly (Fig. 4 and 5) and of the left temporal horn (Fig. 5). There was no shift of the ventricular system to one side or the other (Fig. 6). This finding was consistent with generalized and localized cerebral atrophy, corresponding to the site of the assumed cerebral infarction. The patient withstood the procedure well, and he left the hospital on May 11, 1956, to be maintained on anticonvulsant and hypotensive medication under the care of his family physician.

Fig. 5.—Pneumoencephalogram. Posteroanterior view, with patient in prone position. Note dilatation of left occipital and temporal horns.

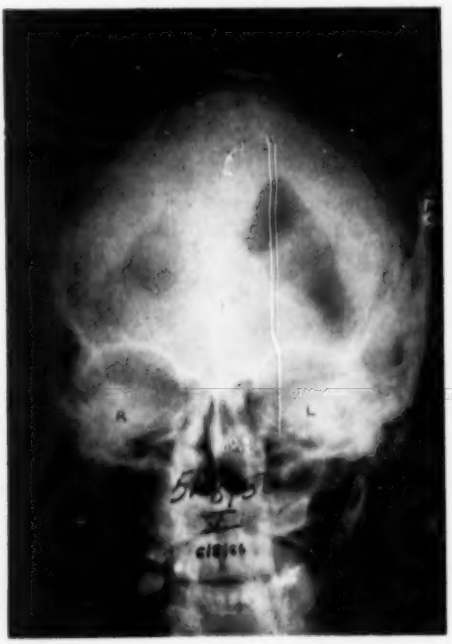


Fig. 6.—Pneumoencephalogram, anteroposterior view, with patient in supine position. Note dilatation of both lateral ventricles. Anterior horns are comparable in size. There is no shift.

Comment

This patient demonstrated the temporal relationship between the onset and course of his assumed cerebral infarction and the displacement of the pineal gland. On the 6th day of his illness the pineal gland was shifted 5 mm. to the contralateral side, and this increased to 7 mm. by the 17th day. Presumably this occurred concomitantly with the presence of cerebral edema following the vascular occlusion. Coincidental with his clinical and electroencephalographic improvement, over a period of 32 days, the pineal gland returned to its normal midline position, corroborating further the impression that the edema had by then subsided. Subsequently, a pneumoencephalogram revealed cerebral and cortical atrophy, most particularly in the left hemisphere posteriorly, as can be seen in Figures 4 and 5, corresponding to the site of the lesion. Although no angiography was performed, it is justifiable on the basis of the air study and the neurological deficit to conclude that an infarction had occurred in the territory supplied by the left middle cerebral artery.

A review of the literature disclosed a relatively small number of similar cases. One paper [18] placed the incidence of pineal shift in 69 patients with vascular hypertension as high as 19%. This has been neither confirmed by others nor borne out in our large number of patients with hypertension.

Ten cases reported by different authors are summarized in the accompanying Table.

The 11 cases listed in the Table may be summarized as follows:

1. Contralateral shift of the pineal gland or the ventricular or the arterial system varied from 2 to 7 mm.

2. The duration from the most recent major episode to the time of x-ray confirmation of the shift varied from 3 to 14 days. In one case the pineal gland was displaced 5 mm. on the 6th day and had returned to its normal midline position 26 days later.

3. In each case one or more major vessels was involved as follows:

(*a*) Internal carotid artery, four cases
(*b*) Internal carotid pus anterior or middle cerebral arteries, two cases
(*c*) Middle cerebral artery, three cases
(*d*) Anterior and middle cerebral arteries, two cases

4. Angiography was performed in seven cases, and a vascular occlusion was demonstrated in five cases.

5. Four patients were subjected to craniotomy, of whom two died postoperatively.

6. Seven patients survived the acute infarction for variable, unstated periods.

It is assumed by most authors that the process of infarction, together with severe ischemia following the vascular occlusion, leads to the formation of cerebral edema. It is quite apparent from the foregoing cases that the edema can be of sufficient degree to simulate a brain tumor. Even in the face of a perfectly typical clinical picture of a vascular incident, one cannot be absolutely certain of the absence of an intracranial mass. This becomes doubly difficult in the presence of a displacement of cerebral structures. Undoubtedly many negative explorations have been performed in similar cases. A further aid in making the correct diagnosis must therefore be sought in carefully observing the clinical course and in carotid angiography, which may demonstrate the occluded vessel.

Summary

A case is reported of unilateral cerebral edema associated with an infarction due to an occlusion in the left middle cerebral artery in which the pineal gland was first shifted 5 mm. and then 7 mm. to the contralateral side, and 15 days later it reverted to its normal midline position. Six months later a pneumoencephalogram demonstrated marked cerebral atrophy at the site of the infarct.

Ten cases in which the pineal gland or the ventricular or the arterial system was displaced to the contralateral side in vascular occlusion previously reported by various authors are summarized.

Summary of Ten Cases Reported by Different Authors and the Present Case of Cerebrovascular Occlusion Simulating an Intracranial Space-Occupying Lesion

Author	Contralateral Displacement			Duration from Most Recent Episode to X-Ray Days	Vessels Involved	Angiography	Craniotomy	Survival*	Chief Neurological Deficit	Postmortem Findings
	Pineal Gland	Ventricles	Cerebral Vessels							
King[11]	3 mm. to l.	Deviation of rt. lateral and third ventricles to l. (ventriculogram)	...	3	Thrombosis at junction of rt. int. carotid and middle cerebral art.	Rt. carotid	Necrotic brain—rt. frontal parietal and anterior temporal areas	Died 48 hr. postop.	L. hemiplegia	Thrombosis in rt. int. carotid artery; rt. ant. and middle cerebral arteries completely occluded; necrosis and softening of brain in rt. frontal, parietal, and ant. temporal areas
Elvidge and Werner[10]	..	Septum pellucidum 4 mm. to rt.; third ventricle, slight shift to rt. (ventriculogram)	..	3	Thrombosis in l. int. carotid art. in neck	L. carotid	...	Yes	Rt. hemiplegia; total aphasia	...
		Septum pellucidum 2 mm. to rt. (pneumoencephalogram)	...	12	Thrombosis of l. int. carotid art.	L. carotid	...	Yes (2 wk. and discharged)	Rt. hemiplegia; motor aphasia	..
		"Slight shift" of septum pellucidum to rt. (pneumoencephalogram)	...	6	Narrowing of intracranial portion of l. into carotid art.	L. carotid	...	Yes	Rt. hemiplegia; motor aphasia	..
Smiley[11]		"Pronounced ventricular shift" from rt. to l., without ventricular deformity (ventriculogram 1 mo. later)		73	Rt. middle cerebral art.	B. carotids	Swelling and softening of rt. cerebral hemisphere	Yes (1 mo. and discharged)	L. hemiparesis; l. homonymous hemianopsia	..
	"Pineal shifted to rt."	...	L. ant. cerebral art. shift from l. to rt.	3	L. ant. and middle cerebral art.	L. carotid	..	Died 24 hr. post-angiography	Rt. hemiplegia; rt. hemianesthesia; aphasia	Massive infarction and swelling of left cerebral hemisphere, including basal ganglia; obstruction at origin of left middle cerebral artery
Strully et al.[11]	On adm. midline; 4 days later:+ 2-3 mm. to rt.; 7 days after adm.: 6 mm. to rt.	...	...	4	Thrombosis l. int. carotid art. in neck	B. carotids	..	Yes	Rt. hemisensory defect; sensory aphasia; rt. homonymous hemianopsia	..
Farmer and Swan-	..	Bodies of lateral ventricles shifted 5 mm. to l.	..	3	Thrombosis rt. middle and ant. cerebral art.	...	Rt. temporal-parietal surface of cortex hyper-	Died 6 hr. postop.	L. hemiparesis; l. hemihypesthesia	Thrombosis of rt. middle and anterior cerebral arteries; encephalomalacia and edema

Jones[5]	(ventriculogram)	"	3	L. int. carotid and L. ant. cerebral art.	"	Softening in L. (frontoparietal areas	Died 3 wk. after onset of illness.	Rt. hemiplegia; rt. hemihypalgesia; rt. homonymous hemianopsia	Thrombosis of L. int. carotid and ant. cerebral arteries
Farmer and Wood[24]	"	Ventricular system shifted 6 mm. to rt. post mortem)	"	"	"	"	Yes (follow-up 4 mo.)	Weakness of lower face and hand on rt.	"
	"	L. lateral ventricle depressed and shifted 5 mm. to rt.	"	714	L. middle cerebral art. territory	"	Yes (follow up 9 mo.)	Rt. hemiparesis; rt. hemihypalgesia; rt. homonymous hemianopsia	"
Present case	6 days: 5 mm.; 17 days: 7 mm.	Six mo. later: marked cerebral atrophy without displacement at site of infarct. (pneumoencephalogram)	"	6	L. middle cerebral art. territory	"			

* Duration of survival not stated in all cases.

Patients with occlusive cerebrovascular disease may present findings simulating an intracranial space-occupying lesion and thereby occasionally undergo needless craniotomy. The clinical course and carotid angiography may help in establishing the correct diagnosis.

Financial assistance for procurement of reprints was provided by the Gray Pharmaceutical Company, Newton, Mass.

150 S. Huntington Ave. (30).

REFERENCES

1. Alpers, B. J.: Clinical Neurology, Philadelphia, F. A. Davis Company, 1946.

2. Baker, A. B., Editor: Clinical Neurology, New York, Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1955.

3. Bing, R.: Textbook of Nervous Diseases, translated and enlarged from the 5th German Edition by Webb Haymaker, St. Louis, C. V. Mosby Company, 1939.

4. Brain, R.: Diseases of the Nervous System, Ed. 5, London, Oxford University Press, 1955.

5. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 3, Springfield, Ill., Charles C. Thomas, Publisher, 1952.

6. Grinker, R. R., and Bucy, P. C.: Neurology, Ed. 4, Springfield, Ill., Charles C. Thomas, Publisher, 1951.

7. Merritt, H. H.: A Textbook of Neurology, Philadelphia, Lea & Febiger, 1955.

8. Nielsen, J. M.: A Textbook of Clinical Neurology, Ed. 3, New York, Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1951.

9. Wechsler, I. S.: Textbook of Clinical Neurology, Ed. 6, Philadelphia, W. B. Saunders Company, 1947.

10. Wilson, S. A. K.: Neurology, edited by Ninian A. Bruce, Ed. 2, Baltimore, Williams & Wilkins Company, 1955.

11. Cairns, H., and Jupe, M. H., in A Text-Book of X-Ray Diagnosis, edited by S. C. Shanks, P. Kerley, and E. W. Twining, London, H. K. Lewis & Co., Ltd., 1939, Vol. III.

12. Davidoff, L. M., and Epstein, B. S.: The Abnormal Pneumoencephalogram, Philadelphia, Lea & Febiger, 1950.

13. Dyke, C. G., and Childe, A. E., in Diagnostic Roentgenology, edited by R. Golden, New York and Edinburgh, Thomas Nelson & Sons, 1936.

14. Ecker, A. E., and Riemenschneider, P. A.: Angiographic Localization of Intracranial Masses, Springfield, Ill., Charles C. Thomas, Publisher, 1955.

15. De Lorimier, A. A.; Moehring, H. G., and Hannon, J. R.: Clinical Roentgenology, Springfield, Ill., Charles C Thomas, Publisher, 1954, Vol. II.

16. Schwartz, C. W., and Collins, L. C.: The Skull and Brain Roentgenologically Considered, Springfield, Ill., Charles C Thomas, Publisher, 1951.

17. Murphy, P. J.: Cerebrovascular Disease, Chicago, Year Book Publishers, Inc., 1954.

18. Jefferson, A.: Hypertensive Cerebral Vascular Disease and Intracranial Tumor, Quart. J. Med. 24:245-268, 1955.

19. King, A. B.: Massive Cerebral Infarction Producing Ventriculographic Changes Suggesting a Brain Tumor, J. Neurosurg. 8:536-539, 1951.

20. Elvidge, A. R., and Werner, A.: Hemiplegia and Thrombosis of the Internal Carotid System, A. M. A. Arch. Neurol. & Psychiat. 66:752-782, 1951.

21. Smiley, G. L.: Occlusive Cerebrovascular Disease Simulating Brain Tumor, A. M. A. Arch. Neurol. & Psychiat. 67:633-640, 1952.

22. Strully, K. J.; Hurwitt, E. S., and Blankenberg, H. W.: Thrombo-Endarterectomy for Thrombosis of the Internal Carotid Artery in the Neck, J. Neurosurg. 10:474-482, 1953.

23. Farmer, T. W., and Swanton, M. C.: Presentation of Case, Clinical Pathologic Conference, Neurology 5:587-593, 1955.

24. Farmer, T. W., and Wood, E. N.: Personal communication to the authors, June, 1956.

Arteriographic Demonstration of the Collateral Circulation of the Cerebral Hemispheres

LESTER A. MOUNT, M.D., and JUAN M. TAVERAS, M.D., New York

The anatomy of the collateral circulation of the major vessels of the brain has been known since the studies of Willis, but little is known about the ability of these and other anastomotic channels not described by Willis to function in patients who have had spontaneous or surgical occlusion of one or more major arterial trunks. The purpose of this presentation is to describe the findings in a series of such cases studied at the Neurological Institute of the Presbyterian Hospital of New York.

The collateral circulation of the cerebral hemispheres has been clearly demonstrated by cerebral angiography in seriographic films obtained on 42 patients who had had surgical therapy for intracranial aneurysms and on 30 patients who had thrombosis of the internal carotid artery or one of its branches. The potential collateral circulation was found to be very extensive but variable. The first, and most important, source of collateral circulation is through the circle of Willis by way of the anterior and posterior communicating arteries, and, of these, the anterior communicating appears to be the dominant contributor. The pattern of the vessels in the circle of Willis is, however, quite variable, and more frequently than not the circle is asymmetrical. Failure of normal development or aberrant origin of the communicating vessels is common, and the collateral supply by these sources is inconstant. Anastomoses among the meningeal branches of the anterior, middle, and posterior cerebral arteries are the second means of collateral circulation and are more extensive than is usually described in books of anatomy. Direct end-to-end anastomoses among these arteries are readily seen in the seriographic arteriograms. The third source is from the external carotid artery to the internal carotid artery by means of anastomoses between these arteries, particularly through the ophthalmic artery, branches of which communicate with the internal maxillary, superficial temporal, and external maxillary; by anastomoses between the middle meningeal artery and the meningeal branch of the internal carotid, and by way of those unscheduled and inconstant arteries which pass through the dura and anastomose with the arteries on the surface of the brain.

Received for publication June 25, 1956.

From the Departments of Neurological Surgery and Radiology, Columbia University College of Physicians and Surgeons, and the Neurological Surgery and Radiological Services of the Neurological Institute, Presbyterian Hospital of New York.

Source I: The Circle of Willis

Thomas Willis, who described the circle which bears his name, also demonstrated its importance in the collateral circulation of the brain. In his "Two Discourses Concerning the Soul of Brutes,"[39] he wrote: We have elsewhere showed, that the cephalick arteries, via the carotids, and the vertebrals do so communicate one with another and all of them in several places, are so ingrafted one in another mutually that if it happen, that many of them should be stopped or pressed together at once, yet the blood being admitted to the head by the passage of one artery only, either the carotid or the vertebral, it would presently pass through all those parts both exterior and interior; which indeed we have sufficiently proved by an experiment, for that ink being squirted in the trunk of one vessel either carotid or vertebral quickly filled all the sanguiferous passages, and everywhere stained the brain itself.

While the general configuration of the circle of Willis is fairly constant, the size of the various components is extremely variable. Riggs,[27] after dissecting 1647 circles of Willis, divided them into eight groups, of which Group I (only 18%) were classified as normal. Group II (6%) were normal but hypoplastic. Group III (25%) had unilateral hypoplasia of an internal carotid artery and/or an anterior cerebral artery, i. e., the part between the internal carotid and the anterior communicating artery. Group IV (16%) showed unilateral hypoplasia of a divisional branch of the basilar artery, which was usually associated with a partial or complete internal carotid origin of the homolateral posterior cerebral artery. Group V (11%) had hypoplasia of both divisional branches of the basilar artery associated with partial or complete internal carotid origin of both posterior cerebral arteries. Group VI (8%) presented combined anatomical variants in both anterior and posterior components of the circle on the same side, unilateral focal hypoplasia of an anterior cerebral artery and hypoplasia of the divisional branch of the basilar artery on the same side, coupled with partial or complete carotid origin of the posterior cerebral artery. Group VII (8%) had bilateral variants of the circle, i. e., unilateral focal hypoplasia of the anterior cerebral part of the circle and hypoplasia of the contralateral divisional branch of the basilar and also partial or complete internal carotid origin of the posterior cerebral artery. Group VIII (8%) showed unilateral focal hypoplasia of the anterior cerebral artery and bilateral hypoplasia of the divisional branches of the basilar artery with partial or complete internal carotid origin of both posterior cerebral arteries. From the foregoing it is evident that variations from the supposed normal are usually present in the circle of Willis.

Although the contribution of the parts of the circle of Willis is variable as a result of the many anatomical deviations, the normal-sized and hypoplastic arteries can enlarge in response to the increased demand for blood following ligation of the cervical portion of the internal carotid artery. In a patient having a normal circle of Willis the collateral supply by way of the anterior communicating artery is the major, and the posterior communicating artery the minor, contributor. This fact was demonstrated arteriographically by the fact that in none of our cases following ligation of the internal carotid artery was the anterior cerebral artery well filled either by way of the posterior communicating artery or by backflow through the ophthalmic artery. It was shown clinically by the fact that all patients with a hypoplastic divisional part of the anterior cerebral artery would not tolerate ligation of the internal carotid artery. Padget,[23] in 1945, described the anterior part of the circle of Willis to be more dependable as a potential source of collateral circulation. In such patients both the anterior and the middle cerebral artery on the ligated side are well shown arteriographically when the opposite carotid artery is injected. Torkildsen and Koppang[36] first described this crossed circulation as demonstrated arteriographically, although this crossing is a widely known fact.

CASE 1.—Collateral circulation via anterior communicating artery.

A 55-year-old woman had sudden onset of headache and then loss of consciousness. On regaining consciousness she vomited and noted weakness in the left upper extremity and the left side of the face. The significant findings on examination were blood pressure 176/86, moderate weakness and reduction of stereognostic and position sense in the left upper extremity, and left facial paresis. Bilateral carotid arteriograms showed a saccular aneurysm of the right middle cerebral artery. The right internal carotid artery was ligated, using a Selverstone clamp. Bilateral carotid arteriography three and a half months later showed the Selverstone clamp to be closed. There was some backflow from the ophthalmic artery into the internal carotid artery and thence into the middle cerebral artery. However, the greatest collateral circulation was from the left side through the anterior communicating artery with good filling of the anterior and middle cerebral arteries on the right.

Comment.—The arteriogram shows that the major supply of blood to the right cere-

bral hemisphere after ligation of the right internal carotid artery was by way of the anterior communicating artery, but there was also a contribution from the external carotid via the ophthalmic.

The blood flow through the various components of the circle of Willis is determined by difference in blood pressure and the cerebrovascular resistance. In a patient having a normal circle of Willis and normal internal carotid and vertebral arteries, there is little blood flow through the communicating arteries. This was demonstrated in 1912 by Kramer,[17] who used living dogs and monkeys and injected small amounts of dye into the common carotid artery after various arterial ligations. He described the circle of Willis as an anteroposterior anastomosis that operates only when either the carotid or the vertebral artery is tied. It is the place where opposing streams from the carotid and vertebral arteries meet; and when the pressures are equal, they do not mix. This is well shown arteriographically (Egas Moniz,[21] 1934) by the absence of filling of the internal carotid system on the opposite side of the head when carotids on one side are injected. The opposite side normally does fill when the contralateral carotid artery has been ligated or is manually compressed at the time of the injection. Further, in patients with a normal circle of Willis, the basilar system is not demonstrated by carotid injection, nor is the internal carotid system shown on vertebral artery injection unless the carotid has been ligated or is compressed at the time of injection.

The posterior communicating artery in a patient having a normal circle of Willis will supply the middle cerebral artery, and occasionally make minor contributions to the anterior cerebral artery (Fig. 1).

CASE 2.—Collateral circulation between the basilar-vertebral and internal carotid systems via posterior communicating artery.

A woman of 49 had had pain in the right eye and the right side of the head for four weeks. Five days before admission to the hospital she developed ptosis, double vision, and throbbing occipital pain. On examination there was complete loss of function of the right third nerve. There were 400 red blood cells per cubic millimeter in the cerebrospinal fluid. Carotid arteriography showed an aneurysm of the internal carotid artery at its junction with

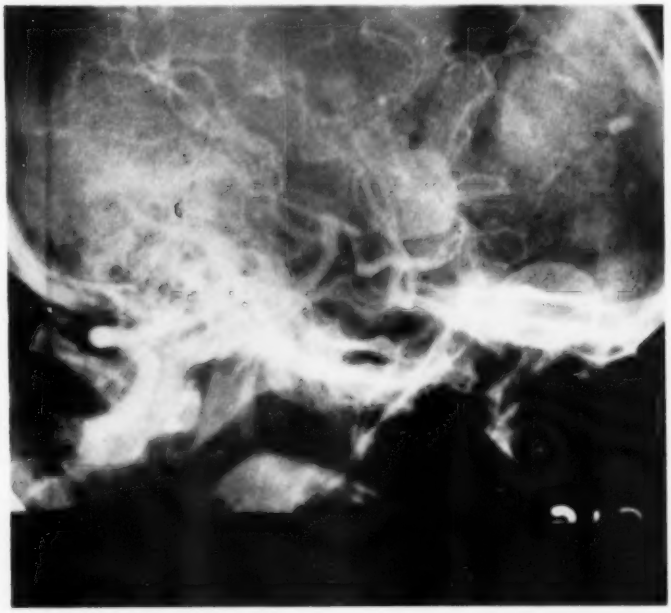


Fig. 1 (Case 2).—Collateral circulation via posterior cerebral artery. Right vertebral arteriogram taken seven months after ligation of the internal carotid artery on the right side shows the right middle cerebral artery to be supplied by way of the enlarged posterior communicating artery.

the posterior communicating artery on the right and a small one on the left at the same site.

Ligation of the cervical portion of the internal carotid artery on the right was performed. Progress bilateral carotid and vertebral arteriography months later (Fig. 1) showed the right middle cerebral artery to fill by way of the right posterior communicating artery, which had enlarged to two and one-half times its previous diameter. The right anterior cerebral artery was filled by way of the anterior communicating artery. The aneurysm on the right was no longer demonstrated.

Comment.—The collateral circulation to the middle cerebral artery in this case was by way of the large posterior communicating artery, and that to the anterior cerebral artery was via the anterior communicating artery. There was a very minor contribution by way of back-flow through the ophthalmic artery.

Variations in the anatomical configuration of the circle of Willis are largely responsible for the blood flow through its various components to the anterior, middle, and posterior arteries. When the first part of one anterior cerebral artery is hypoplastic, the major blood supply to both anterior cerebral arteries is through the opposite anterior cerebral artery by way of the anterior communicating artery. This was demonstrated arteriographically in a patient in whom both anterior cerebral arteries were shown on left carotid injection without compression of the right carotid. On injection of the right carotid only the middle cerebral artery was demonstrated. However, when the left carotid was injected and the right was compressed, both anterior and both middle cerebral arteries were shown. The first part of the anterior cerebral artery on the right side was very small in caliber.

Case 3.—A 38-year-old man had sudden onset of headache and vomiting two weeks before admission. Examination revealed blood pressure 150/122, papilledema with hemorrhages, and retinal arteriosclerosis. Bilateral carotid arteriography showed an aneurysm on the right at the bifurcation of the internal carotid into anterior and middle cerebral arteries and junctional dilatation on the left at the site of origin of the anterior choroidal artery. The right anterior cerebral artery was not demonstrated when right carotid arteriography was performed, and both anterior cerebral arteries were demonstrated when left carotid arteriography was performed without compression of the right carotid arteries. However, when the right carotids were compressed and the left side was injected, both anterior and middle cerebral arteries were filled. The right anterior cerebral artery between the internal carotid and the anterior communicating artery was small, about one-half the size of that on the left. A ligation of the right common carotid was performed without complications.

Comment.—There was little or no blood flowing through the hypoplastic divisional branch of the right anterior cerebral artery; but when the pressure was lowered on the right side of the circle of Willis by compressing the right carotid arteries, blood

Fig. 2 (Case 4).—Deficient circulation through right anterior cerebral artery between internal carotid and anterior communicating artery; internal carotid origin of posterior cerebral artery.

In the original right carotid arteriogram the right anterior cerebral artery was never shown. Five separate injections, with and without compression of the carotid arteries on the left side during injection, were made, and seriographic films were taken. The right carotid arteriogram taken eight months after partial ligation of the left carotid is shown above. Both anterior cerebral arteries are now filled through a small divisional portion of the right anterior cerebral artery. This suggests that the anterior cerebral artery is now larger than it was previously, although still smaller than normal. Note that both posterior cerebral arteries filled. The patient again did not tolerate a second attempt at complete closure of the left internal carotid artery.

flowed through the hypoplastic segment and filled the middle cerebral artery.

The carotid origin of the posterior cerebral artery is another variation of the circle of Willis which influences the collateral circulation. A small communication between the posterior cerebral artery and the vertebral basilar system may be present. This anomaly, the carotid origin of the posterior cerebral, in association with other anomalies of the circle is present in 51% of patients, according to Riggs' statistics.[27] It adds to the risk of insufficient immediate collateral circulation following carotid ligation.

CASE 4.—Inadequate collateral circulation as result of abnormalities in the circle of Willis. Internal carotid origin of the posterior cerebral artery and deficient divisional part of the anterior cerebral artery on the same side.

The patient was a 43-year-old, left-handed woman who had a subarachnoid hemorrhage. Examination showed slight weakness in the right upper extremity and slight expressive aphasia. Bilateral carotid arteriography showed bilateral multilocular middle cerebral aneurysms, those on the left being larger than that on the right. Both anterior cerebral arteries were filled from the left side. The segment of the right anterior cerebral artery between the internal carotid and the anterior communicating artery was not demonstrated from either side, even when the opposite side was compressed at the time of the injection, and there was an internal carotid origin of the posterior communicating artery. A Selverstone clamp was placed on the left internal carotid artery; but whenever complete closure of the clamp was attempted, the patient developed weakness in the right extremities. The clamp was closed until the artery was open only 1 mm. Two months after the patient was discharged she developed left-sided headache. Eight months after operation she had bilateral carotid arteriography. The size of the aneurysms was unchanged. The Selverstone clamp was not causing complete occlusion of the left internal carotid artery. While on the original films there was no filling of the anterior cerebral arteries from the right side, both anterior cerebral arteries filled now from the right side without compression of the left carotid (Fig. 4*B*). This indicated opening of the hypoplastic anterior cerebral artery and suggested that the patient might now have sufficient collateral circulation for complete ligation of the left internal carotid artery. However, 28 hours after complete ligation the patient developed right hemiplegia and aphasia, from which she is making a slow recovery.

Comment.—The collateral circulation to the middle cerebral artery on the left side was inadequate even after the hypoplastic divisional part of the right anterior cerebral artery had enlarged enough to supply both anterior cerebral arteries. Apparently the posterior communicating artery on the left side was deficient also. The posterior cerebral artery on the right had a carotid origin.

Absence of major contributing vessels of the circle of Willis has been reported by Fisher in 1913,[12] by Lowrey in 1945,[19] and by others. Fisher reported the complete absence of both internal carotid arteries. Takahashi, in 1940,[33] related the case of a 28-year-old woman who had complete closure of both common carotid arteries as a result of thromboangiitis obliterans. A vertebral arteriogram in this case demonstrated the carotid, as well as the vertebral, system intracranially. Frøvig, in 1946,[13] reported a similar case in which arteriography was performed but the arteriogram was not satisfactory. He cited references to 11 cases of bilateral obliteration of the common carotid arteries, the earliest in 1847. Wood, in 1857, reported two cases of bilateral common carotid artery ligation, the first performed by Van Buren, who ligated the second side in 1850, six years after ligating the first. In the second case, the second side was ligated 171 days after the first. Riegner, in 1884,[26] described the ligation of both common carotid arteries in stages one year apart. Ray, in 1941,[25] reported two patients who had had ligation of both common and external carotid arteries in the treatment of arteriovenous aneurysms. One patient died who had ligation of the common and external carotid arteries on one side and, 14 months later, ligation of those on the other side. In the patient who lived, the common and external carotid arteries on the right were ligated. Eight months later the internal carotid on the left was ligated, and then, 13 days after that, the left external carotid artery was ligated.

A similar case was treated at the Neurological Institute. The patient, an 11-year-old girl (Case 5), had the common and external carotid arteries ligated on the left, the side of the large intracerebral arteriovenous angioma, and seven years later had the right external and internal carotid arteries and the left and right occipital arteries ligated in one stage. At the time of the second ligation not only was the right internal carotid artery supplying blood to the left cerebral hemisphere and to the arteriovenous angioma but also both occipital arteries, which penetrated the skull to supply blood directly to the angioma. This patient did not have progress arteriography after the second operation, but the major blood supply to the cerebral hemispheres in this case, as well as the others, as described above, must have been by way of the vertebral-basilar system, largely through the posterior communicating arteries.

Case 5.—Both internal and external carotid arteries ligated and hence the blood supply to entire brain via vertebral arteries (courtesy Dr. J. Lawrence Pool).

This patient was first admitted to the Neurological Institute at the age of 11 years with a four-year history of recurrent attacks of severe dull, throbbing headaches in the left frontal region, lasting 10 to 15 minutes and occurring once a month, with occasional vomiting or transient weakness of the right extremities accompanying the headaches. She had a right-sided convulsion six days before admission and had had persistent weakness of the right extremities since that time. Her father had noted prominent pulsations in the left side of her neck for two years. Examination showed right hemiparesis and right homonymous hemianopsia. A bruit could be heard over the left temporal region, which was reduced in intensity by left carotid compression. X-rays showed increased vascularity of the skull and hairline streaks of calcification in the left posterior temporal region. A pneumoencephalogram showed enlargement of the left lateral ventricle. The left internal, external, and common carotid arteries were ligated.

The patient was only temporarily improved by her operation. The bruit reappeared in 15 days. Numbness of the right side of her body appeared about one month after operation. All the symptoms continued for an additional seven years, until the patient's second admission. Six months before her second admission she had noted a pins-and-needles sensation on both sides of the body when she cried. Examination showed her blood pressure was 125/55. There were atrophy of the extremities, hemiparesis (60% of normal), hyperreflexia, impairment of sensation, and homonymous hemianopsia, all on the right side. X-rays showed marked vascularity of the cranial vault with many wide vascular channels, some as wide as 5 mm.

Arteriography.—Via Right External Carotid Artery: The greatest flow was into the occipital artery. The artery was large in size and crossed the midline, entered the skull, and emptied into the posterior part of the large arteriovenous angioma.

Via Right Internal Carotid Artery: The right anterior cerebral artery was very large, as was the anterior communicating artery. A large portion of the contrast material crossed the midline into the anterior and middle cerebral arteries, and from there passed into the anterior part of the arteriovenous angioma.

Via Left Occipital Artery: The artery was large. As it reached the base of the skull, it divided into a number of very large vessels, which corresponded to deep grooves in the left posterior parietal and occipital bones. Some of these vessels pierced the skull and emptied into the angioma in the parietal and occipital regions.

Operation.—The left occipital artery, the right internal carotid artery, and the right external carotid artery were ligated. The patient tolerated the procedure without complications.

Comment.—Before the second operation the left cerebral hemisphere was supplied with blood by way of the anterior communicating artery, as well as both occipital arteries via retia mirabilia (Batson[1]). After the second operation the blood supply to both cerebral hemispheres must have come from the vertebral-basilar system by way of the posterior communicating arteries. There was doubtless some back-flow through the ophthalmic arteries also.

Persistent carotid-basilar anastomosis, while not an anomaly of the circle of Willis, does have a considerable influence on the collateral circulation through the circle of Willis. Actually, it should improve the collateral circulation when cervical carotid ligation is performed or when thrombosis of the cervical internal carotid artery occurs. It would possibly nullify the results of cervical carotid ligation in the treatment of intracranial aneurysms were the aneurysms to be on the same side as the anastomosis.

It has been identified by Padget [23] in the 3-4 mm. stage as a branch of the primitive internal carotid artery which contributes to the bilateral channels that join to form the basilar arteries.

CASE 6.—Persistent carotid-basilar anastomosis. A 42-year-old man had sudden onset of sharp pain behind the left eye five days before admission. The next day he had double vision, and the day after that he noted drooping of the left upper eyelid. Examination showed complete paralysis of the left third nerve. Left carotid arteriography showed an aneurysm of the left internal carotid artery. Right carotid arteriography showed persistent internal carotid-basilar anastomosis. The left internal carotid artery was ligated with a Selverstone clamp without complications.

Source II: Anastomoses Among Anterior, Middle, and Posterior Cerebral Arteries

Heubner,[14] in 1872, demonstrated arterial communications among the distal branches of the anterior, middle, and posterior cerebral arteries by injecting colored fluids. In 1907 Beevor [2] described the arterial supply of the brain, which he demonstrated by simultaneously injecting the vessels with colored gelatin. Fay,[11] in 1925, tied the circle of Willis, injected the middle cerebral artery with mercury, and took stereoscopic x-ray pictures of the brain. He found that the entire brain, as far as the cortex was concerned, became completely injected. Thus, he illustrated a wider range of communications than was previously thought to exist. Cobb,[5] in 1931, stated that there are no end-arteries in the brain, even in the basal ganglia. In 1953, vander Eecken and Adams,[37] in a very fine paper, described the anastomoses between the major arteries of the brain and their branches in human cadavers. They demonstrated end-to-end anastomoses between the pre-Rolandic branch of the middle cerebral artery and the posterior internal frontal branch of the callosomarginal branch of the anterior cerebral artery, in the precentral sulcus; between the Rolandic branch of the middle cerebral artery and the paracentral branch of the anterior cerebral artery, in the central sulcus, and between the anterior division of the anterior parietal, or post-Rolandic, branch of the middle cerebral artery and the precuneal branch of the anterior cerebral artery, in the postcentral sulcus. Further, they showed smaller connecting channels between the orbital branches of both arteries; between the anterior orbitofrontal branches of the middle cerebral artery and the distal branches of the frontopolar division of the anterior cerebral artery; between the upper branches of the orbitofrontal division of the middle cerebral artery and the anterior and middle internal divisions of the anterior cerebral artery, and between the upper branches of the anterior parietal division of the middle cerebral artery and the precuneal division of the anterior cerebral artery.

End-to-end anastomoses between the middle and posterior cerebral arteries were also described in the superoterminal portion of the parieto-occipital sulcus or in the inferior portion of the interparietal sulcus between the angular or the posterior temporal branches of the middle cerebral artery and the parieto-occipital branch of the posterior cerebral artery, and small communications between the anterotemporal branch of the posterior cerebral artery and the anterotemporal branch of the middle cerebral artery, or branches.

End-to-end anastomoses between the anterior and posterior cerebral arteries are located in the anterior part of the parieto-occipital sulcus between the precuneal or posterior callosal branches of the anterior cerebral artery and the parieto-occipital branch of the posterior cerebral artery. Anastomoses between the two anterior cerebral arteries, in addition to a single anterior communicating artery, were found in many cases. Further, communications between the pericallosal or callosomarginal arteries on the two sides were occasionally found.

Communications among the anterior, middle, and posterior cerebral arteries have been shown arteriographically. Krieg,[18] in 1939; and Raney, Raney, and Sanchez-

Perez,[24] in 1949, noted filling of the middle cerebral branches from anterior cerebral divisions. In a comprehensive article, Ethelberg,[10] in 1951, described changes in circulation through the anterior cerebral artery. He mentioned collateral circulation from peripheral branches of the anterior and posterior cerebral arteries to peripheral branches of the middle cerebral artery, and some of these were demonstrated arteriographically. Schurr and Wickbom,[30] in 1952, in an article on rapid serial angiography, discussed one case of middle cerebral artery thrombosis in which the arteriogram showed filling of ascending branches of the middle cerebral artery from the anterior cerebral artery. Mount and Taveras,[22] in 1953, described, as one of the sources of collateral circulation, anastomoses on the surface of the brain among the anterior, middle, and posterior cerebral arteries, as shown in seriographic arteriograms. Rosegay and Welch,[28] in 1954, also demonstrated arteriographically peripheral collateral circulation among the cerebral arteries. In 1955, Welch, Stephens, Huber, and Ingersoll[38] illustrated collateral circulation from the anterior to the middle cerebral arteries following middle cerebral branch occlusion.

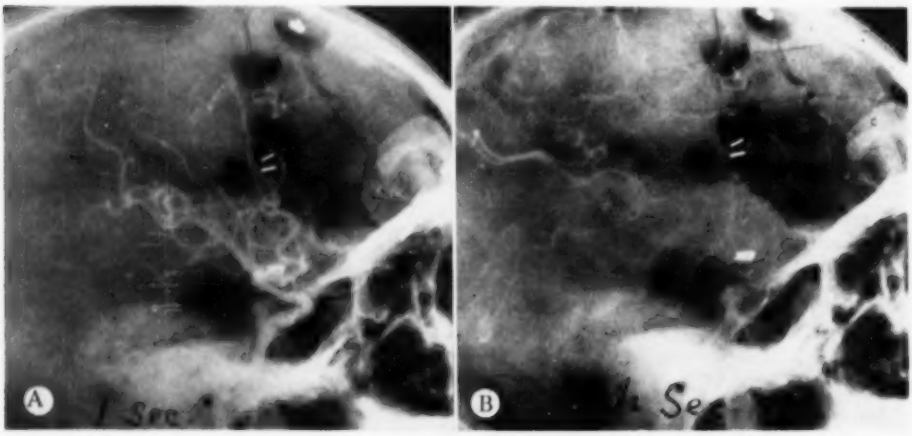
The collateral circulation among the peripheral branches of the anterior, middle, and posterior cerebral arteries, so well described anatomically by vander Eecken and Adams,[37] has been demonstrated arteriographically by us in patients who had previously had various arterial ligations in the neck or intracranially for the treatment of intracranial aneurysms or in patients having thrombosis of the middle cerebral artery. Collateral circulation has been shown extending from the middle to the anterior cerebral artery (Case 7), from the anterior to the middle cerebral artery (Case 8), from the posterior cerebral to the anterior and middle cerebral arteries, and between the right and left pericallosal arteries (Case 9). In the seriographic arteriograms it is possible to follow the blood flow through the anastomotic vessels from one arterial distribution into the adjacent one, and at times even back into the main arterial trunk.

Case 7.—Collateral circulation from the middle cerebral artery to the anterior cerebral artery. (This case is reported by courtesy of Dr. John E. Scarff.)

A 47-year-old man had ligation in two stages of both anterior cerebral arteries in the region of the anterior communicating artery for the treatment of a previously ruptured aneurysm of the

Fig. 3 (Case 7).—Collateral circulation from middle to anterior cerebral artery.

A, the one-second seriographic arteriogram shows the middle cerebral artery well filled but with no filling of the anterior cerebral artery. *B*, the arteriogram taken at two and one-half seconds shows (*a*) the callosomarginal, (*b*) the pericallosal branches of the anterior cerebral, and (*c*) the frontopolar.



anterior communicating artery. A left carotid arteriogram was performed 13 days postoperatively. The one-second arteriographic film (Fig. 3*A*) showed the middle cerebral artery and its branches well outlined but no filling in the anterior cerebral artery or its branches. In the later films, it was possible to identify the anastomoses between the pre-Rolandic branch of the middle cerebral artery and the posterior internal branch of the callosomarginal artery; between the Rolandic branch of the middle cerebral artery and the paracentral branch of the anterior cerebral artery, and between the fine upper twigs of the candelebra of the orbitofrontal branch of the middle cerebral artery and the anterior and middle internal frontal branches of the anterior cerebral artery. In the film taken at two and one-half seconds (Fig. 3*B*) the pericallosal and callosomarginal branches of the anterior cerebral arteries were well demonstrated.

Comment.—Both anterior cerebral arteries could be ligated in this case because the patient had direct anastomoses between the branches of the anterior and middle cerebral arteries which were sufficiently large to carry an adequate amount of blood to the anterior cerebral distribution.

CASE 8.—Collateral circulation from anterior cerebral artery to middle cerebral artery. (This case is reported by courtesy of Dr. Thomas Bridges.)

A 54-year-old woman had rapid onset of hemiplegia following a radical neck dissection for carcinoma of the tongue. In the arteriogram, only a stub of the middle cerebral artery was seen in the anteroposterior view. In the early lateral films in the arteriographic series (Fig. 4) only the anterior cerebral artery and its branches were visualized, and none of the middle cerebral artery was seen, presumably because of thrombosis. In the later films (Fig. 5*A*) direct end-to-end anastomosis between the paracentral branch of the anterior cerebral and the Rolandic branch of the middle cerebral artery was clearly seen, and the entire Rolandic division was well demonstrated. In addition, smaller communications were visualized between the posterior internal frontal branch of the callosomarginal, as well as the paracentral branch of the pericallosal artery, and the pre-Rolandic branch of the middle cerebral artery. The pre-Rolandic branch was well filled. Fine communications were also demonstrated among the posterior, middle, and anterior internal frontal branches of the pericallosal artery, as well as the frontopolar and the orbitofrontal branches of the middle cerebral artery (see also Fig. 8*B*).

Comment.—Direct anastomoses were demonstrated among the various branches of the anterior and middle cerebral arteries posteriorly as far as the Rolandic fissure.

CASE 9.—Collateral circulation from the posterior cerebral artery to the anterior and middle cerebral arteries.

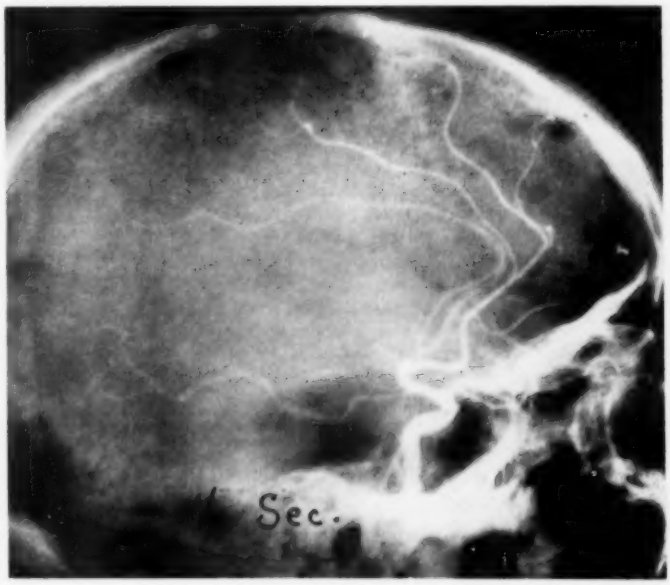


Fig. 4 (Case 8).—Collateral circulation from anterior to middle cerebral artery (see Fig. 5). The one-half-second seriographic arteriogram shows the anterior cerebral artery, the posterior cerebral artery, but no middle cerebral artery, owing to spontaneous thrombosis of this vessel.

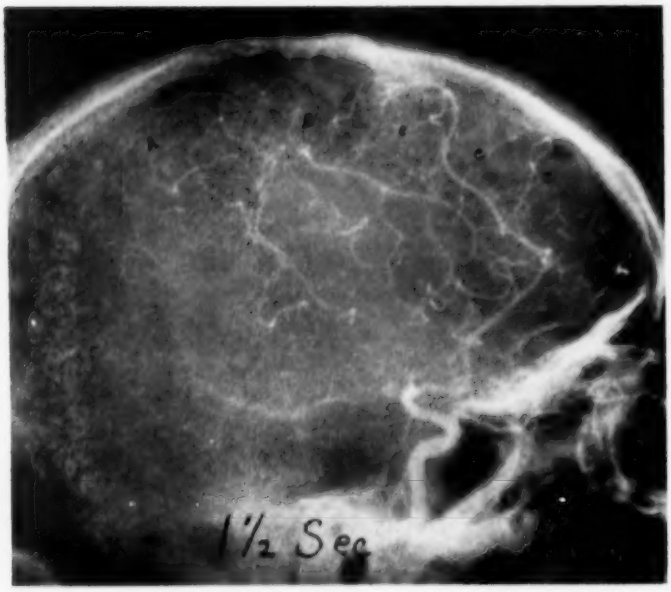


Fig. 5 (Case 9).—Seriographic film taken at one and one-half seconds, showing anastomoses between the anterior and the middle cerebral artery. End-to-end communications between the paracentral branch of the pericallosal division of the anterior cerebral and the Rolandic branch of the middle cerebral (*A*). Small, direct anastomoses between the paracentral, as well as the posterior internal frontal branch of the callosomarginal, and the pre-Rolandic branch of the middle cerebral artery (*B*). Fine communications among the posterior, middle, and anterior internal frontal branches of the callosomarginal and the orbitofrontal of the middle cerebral (*C*). Fine anastomoses between the frontopolar and the orbitofrontal (*D*).

A 59-year-old man had a large aneurysm of the right internal carotid artery which was treated by ligation of the right cervical internal carotid artery. The seriographic arteriogram was taken four months after the ligation (Figs. 9, 10, and 11). There was considerable increase in the size and the number of branches of the anterior temporal and posterior temporal (Fig. 11) divisions of the posterior cerebral artery, and a small end-to-end anastomosis between the anterior temporal branches of the posterior cerebral and of the middle cerebral artery could be seen in the arteriogram. Direct anastomoses were seen between the calcarine branch of the posterior cerebral and the posterior temporal branch of the middle cerebral artery and between the parieto-occipital and the angular artery. End-to-end anastomosis between the parieto-occipital and the posterior parietal artery was well demonstrated. Fine communications were seen between an unnamed branch of the posterior cerebral (artery of the splenium) and the pericallosal artery, with excellent filling of the posterior one-half of the pericallosal artery and its branches, the precuneal and paracentral. There also was a small anastomosis between a branch of the posterior cerebral and a branch of the anterior cerebral artery in the cingulate sulcus (Fig. 11*A* and *B*).

Comment.—In this case it was possible to demonstrate direct anastomoses between every major branch of the posterior cerebral artery and the adjacent branches of the

Fig. 6.—Photograph of a dissected specimen as seen from above. The same direct communications can be seen here, as in the preceding angiogram. (Order of the letters designating the arteries is reversed.) Reproduced from article by H. M. vander Eecken and R. D. Adams,[29] published in *Journal of Neuropathology and Experimental Neurology*, by Waverly Press, Baltimore.

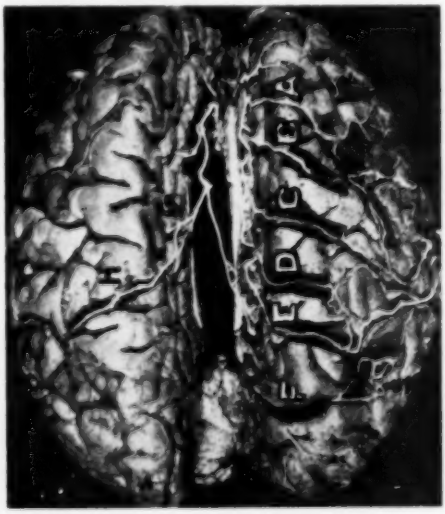


Fig. 7 (Case 9).—Collateral circulation from posterior cerebral artery to middle and anterior cerebral arteries. Preligation vertebral arteriogram. Note the extent of the visualization of the posterior cerebral artery and the size of the posterior cerebral artery, as well as of its main branches, the anterior temporal (*A*), posterior temporal (*B*), calcarine (*C*), and parieto-occipital (*D*). Compare with the postligation arteriogram (Fig. 9).

Fig. 8 (Case 9).—Basal view of a vertebral angiogram taken four months after ligation of right internal carotid artery (note Selverstone clamp in neck). The right posterior cerebral artery is considerably larger than the left. The posterior communicating artery (arrow) is small because, apparently, the collateral circulation is taking place via the superficial arterial anastomosis (see Fig. 9).

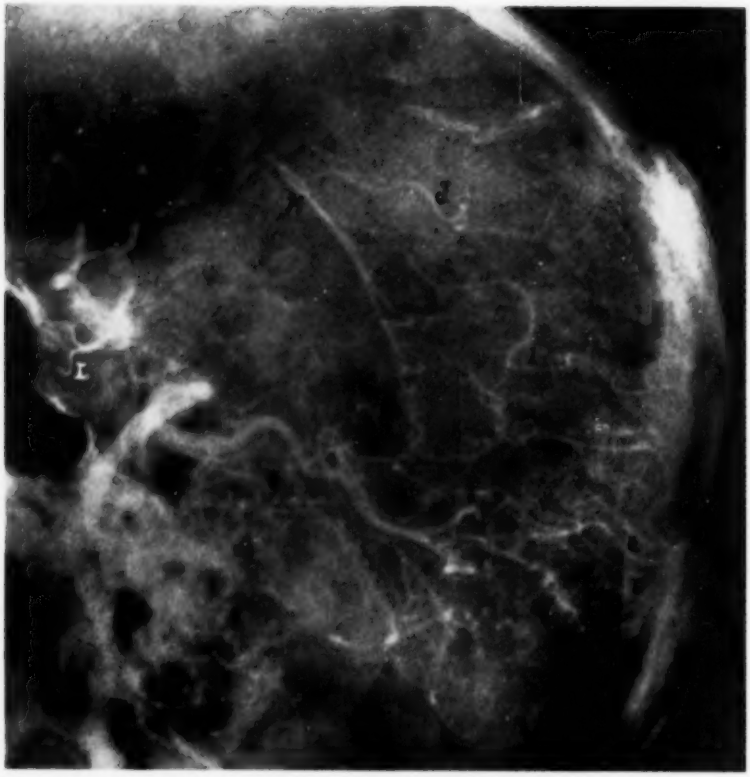
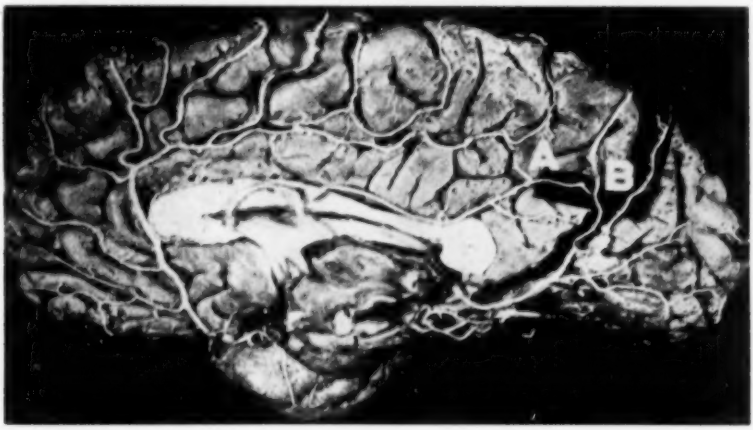


Fig. 9 (Case 9).—*A*, vertebral arteriogram taken at same time as Figure 8 (four months after carotid ligation). Considerable increase in the size and number of vessels in the distribution of the anterior temporal artery (*A*) and posterior temporal artery (*B*) is seen. Enlarged calcarine (*C*) and parieto-occipital branches (*D*) and direct anastomoses (*E*) with the distal branches of the posterior temporal and angular arteries of the middle cerebral group. Direct end-to-end anastomosis (*F*) between the parieto-occipital and the posterior parietal branch of the middle cerebral artery. Fine communications (*G*) between an unnamed branch (artery of the splenium?) of the posterior cerebral artery and the pericallosal of the anterior cerebral artery, with excellent filling of the pericallosal (*H*) and its branches, the precuneal (*I*) and the paracentral (*J*). A small anastomosis between the posterior and the anterior cerebral arteries (*K*) in the cingulate sulcus. A small end-to-end anastomosis (*L*) between the anterior temporal branches of the posterior and the middle cerebral artery.

B, photograph of a specimen showing direct anastomoses between the posterior and middle cerebral arteries (*A*) and the pericallosal and posterior cerebral arteries (*B*). Reproduced from article by H. M. vander Eecken and R. D. Adams,[28] published in *Journal of Neuropathology and Experimental Neurology*, by Waverly Press, Baltimore.



middle and anterior cerebral arteries, as described above and shown in Figure 9.

Demonstration of Collateral Circulation Between Right and Left Pericallosal Arteries

A communication between the right and left pericallosal arteries was shown in Case 9, described above, when left carotid arteriography was performed four months after ligation of the right cervical internal carotid.

Source III: Anastomoses Between External and Internal Carotid Arteries

A. By Way of Ophthalmic Artery

Elschnig,[8,9] in 1892 and 1893, demonstrated that dye injected into the external carotid artery appeared in the ophthalmic artery in cadavers. Bergstrand, Olivecrona, and Tönnis, in 1936,[3] and Ray,[25] in 1941, as well as others, described the details of this collateral circulation.

Possible means of collateral circulation from the external to the internal carotid arteries via the ophthalmic artery are the external maxillary, the internal maxillary, and the superficial temporal. The lateral nasal and angular branches of the external maxillary artery anastomose with the dorsal nasal and palpebral branches of the ophthalmic artery. The internal maxillary artery joins with the lacrimal branch of the ophthalmic artery by way of the middle meningeal. In addition, the deep temporal branches of the internal maxillary artery connect directly with the lacrimal and, through the temporal bone, with the middle meningeal and thence with the lacrimal. The infraorbital branch of the internal maxillary also anastomoses with the ophthalmic. The sphenopalatine branch of the internal maxillary, through its lateral nasal branches, anastomoses with the anterior and posterior ethmoidal branches of the ophthalmic. The superficial temporal connects with the lacrimal and palpebral branches of the ophthalmic by the zygomatico-orbital branch and with the lacrimal and supraorbital branches of the ophthalmic by way of the frontal branch.

Although anatomically there are anastomoses of the external carotid artery with the ophthalmic artery by way of the external maxillary, the internal maxillary, and the superficial temporal arteries, arteriography has demonstrated that the greatest contributor in this triplicity is the internal maxillary. The internal maxillary artery, together with its middle meningeal, deep temporal, and infraorbital branches, as well as the ophthalmic artery, have been shown to have enlarged two to three times their previous size in the arteriograms when the films taken before ligation of the cervical internal carotid artery are compared with those taken after the ligation. On the other hand, the superficial temporal and external maxillary arteries have remained the same size as, or are only slightly larger than, they were before the ligation. When the diameter of the lumen of an artery is doubled, the area of the lumen is increased four times. Therefore, the capacity of the artery is correspondingly increased.

Marx,[20] in 1949, published the arteriographic demonstration of this collateral circulation in patients with thrombosis of the internal carotid artery. This was also shown by Seaman, Page, and German,[31] in 1949; by Denny-Brown,[7] in 1951, and by Sachs,[29] in 1954. Taveras and Mount, in 1953,[22] and 1954,[34] demonstrated this collateral in seriographic arteriograms taken of patients who had previously had the internal carotid artery ligated for the treatment of intracranial aneurysms.

Case 11.—Collateral circulation between the external and the interior carotid arteries by way of back-flow through the ophthalmic artery.

A 53-year-old woman was admitted to the Neurological Institute with an eight-day history of drooping of the right upper eyelid. The night before admission she developed pain in the right eye and right side of the forehead, double vision, headache, nausea, vomiting, and stiffness of the neck. On examination her pulse was 60, respirations 20, and blood pressure 200/90. There were complete dysfunction of the right third nerve and 57,000 red blood cells per cubic millimeter in the cerebrospinal fluid.

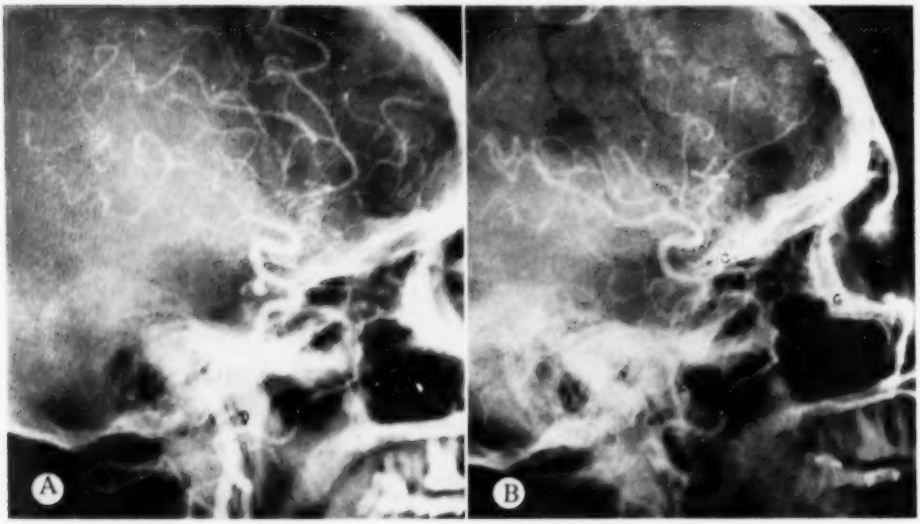


Fig. 10 (Case 11).—Demonstration of back-flow from external to internal carotid through ophthalmic artery.

A, preoperative seriographic arteriogram; *B*, postoperative seriographic arteriogram, four months after carotid ligation. Note enlargement of ophthalmic artery (*C*), internal maxillary artery (*D*), middle meningeal artery (*E*), deep temporal artery (*F*), and infraorbital (*G*) artery. Note the comparative size of these arteries before and after ligation of the internal carotid artery. Note also that the aneurysm is no longer demonstrated.

Arteriography performed 10 days later showed a saccular aneurysm of the internal carotid artery at the junction with the posterior communicating artery (Fig. 10*A*). It measured 1.0 by 0.7 cm. The right cervical internal carotid artery was ligated with a Selverstone clamp. Four months later an arteriogram showed the internal carotid artery to be completely ligated (Fig. 10*B*). The internal maxillary artery and its middle meningeal, deep temporal, and infraorbital branches were enlarged to about twice their previous sizes, and the ophthalmic artery was about two and one-half times its previous diameter. The internal carotid artery in the region of the sella turcica and the middle cerebral artery were well demonstrated in the late arterial phase. The aneurysm was no longer visualized.

Comment.—This case illustrates the enlargement of the anastomosing arteries in an attempt to increase the collateral circulation, especially the internal maxillary and its branches, the middle meningeal, deep temporal, and infraorbital, as well as the ophthalmic artery.

Progress arteriography in all 21 patients who had had ligation of the cervical internal carotid artery only showed back-flow through the ophthalmic artery in all cases, although the degree of the back-flow was variable. This demonstrates the ever-present collateral circulation of the brain through the ophthalmic artery. In none of the cases did the contrast material satisfactorily outline the anterior cerebral artery. Only the middle cerebral arterial tree was well shown, in addition to the internal carotid artery adjacent to the sella turcica. This, again, emphasizes the importance of the collateral circulation by way of the anterior part of the circle of Willis.

B. By Back-Flow from External into Internal Carotid Artery When Common Carotid Artery Is Ligated

When the common carotid artery is ligated, the direction of the blood flow in the first part of the external carotid artery usually is reversed, so that blood flows from the external carotid into the internal carotid in an effort to supply the brain with a sufficient amount of blood. There are rich anastomoses among the branches of the external carotid of the same and opposite

sides, as well as with the vertebral artery and the branches of the thyrocervical trunk. An especially rich collateral supply comes from the inferior thyroid artery to the superior thyroid, and thence into the external carotid.

The rich potential collateral circulation is believed by many to make ligation of the common carotid artery a safer procedure than ligation of the internal carotid. This collateral supply may not be immediately available, and the blood may actually be flowing from the internal carotid into the external carotid. This was shown by Sweet and Bennett [32] in 1948 and was confirmed by Brackett and Mount [4] in 1950. However, Jefferson [15] pointed out that, although the flow may be from the internal carotid into the external carotid in some cases immediately after ligation of the common carotid, the direction of the blood flow will be from the external carotid into the internal carotid in a short time. How soon this occurs will depend upon the relative richness of the collateral circulation of the two arteries.

Arteriograms obtained by insertion of the needle into the internal carotid artery above the ligated common carotid artery show merely the usual external and internal carotid artery distributions, and no conclusion as to the direction of flow could be drawn. The following case gives indirect evidence of the back-flow from the external carotid artery into the internal carotid.

CASE 12.—Indirect demonstration of the back-flow from the external carotid at the bifurcation of the common carotid artery.

Three years before admission this 49-year-old woman had sudden onset of headache, followed by a convulsion and then coma, which lasted 24 hours. On recovering consciousness, she had a left hemiparesis, and blood was found in the spinal fluid. Right-sided headache and mental changes appeared two and one-half years prior to admission. The hemiparesis slowly improved for two years and then began to get worse. Examination showed spastic left hemiparesis and rotatory nystagmus on left lateral gaze. X-rays of the skull revealed calcification in the right internal carotid artery, and carotid arteriography showed an aneurysm, measuring 30 by 17 by 17 mm., at the bifurcation of the right internal carotid artery into the middle and anterior cerebral divisions. Ligation of the right common carotid artery was performed. Progress seriographic arteriography performed four months later by way of the left common carotid artery showed the left internal carotid distribution and right anterior cerebral artery; but when the right external and internal carotid arteries were compressed, both middle and both anterior cerebral arteries, and the right internal carotid artery in the parasellar region, were filled and no aneurysm was demonstrated. A right internal carotid arteriography was unsuccessful, since the lumen of the internal carotid artery could not be entered with the needle.

Comment.—This case indirectly demonstrates the back-flow from the external carotid into the internal carotid at the bifurcation of the common carotid, since internal carotid compression on the side of the ligated common carotid artery so lowered the pressure in the internal carotid adjacent to the sella and in the middle cerebral artery that they filled from the other side, whereas before compression only the left middle cerebral and both anterior cerebral arteries were shown. It is possible that some of the back-flow may have been through the ophthalmic, but were any great portion contributed via the ophthalmic, it is doubtful that carotid compression on one side would have had much effect on lowering the pressure in the internal carotid, and hence promoting better filling in the arteriogram.

C. By Anastomoses Between Meningeal Branch of Internal Carotid Artery and Middle Meningeal Artery

Anastomoses between these two arteries have been described by anatomists and have been shown arteriographically by Denny-Brown [7] in a patient who had occlusion of the right internal carotid artery in the neck and carotid canal.

CASE 13.—Anastomoses between the meningeal branch of the internal carotid artery and the middle meningeal artery.

This 56-year-old woman had the signs and symptoms of an internal carotid artery-cavernous sinus fistula on the left, but the arteriogram had demonstrated its presence on the right side two years before the present admission. She had been treated by ligation of the right cervical internal carotid

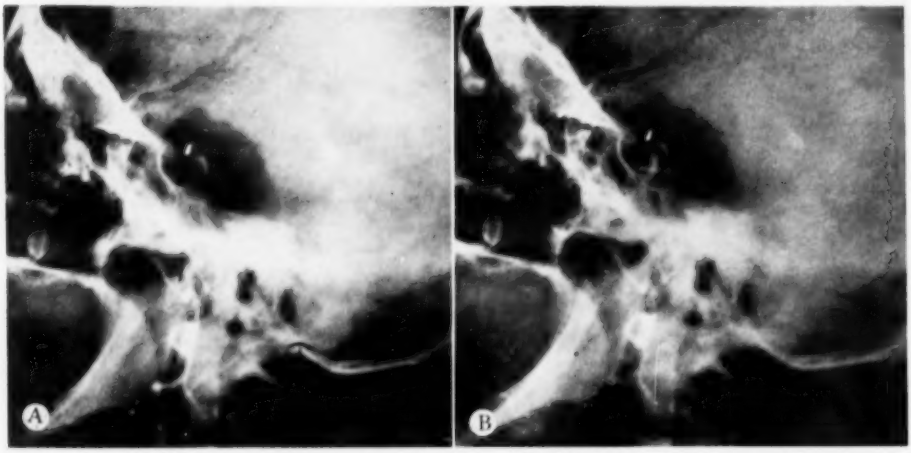


Fig. 11 (Case 13).—Demonstration of collateral circulation from middle meningeal to internal carotid artery via meningeal branch of internal carotid.

A, the one-second seriographic film shows the external carotid and the enlarged middle meningeal artery. *B*, the two-second film shows the internal carotid artery (*D*) (the exact position of the internal carotid is shown in the preoperative films), and a small amount of iodopyracet (Diodrast) in the cavernous sinus (*E*).

artery and the right internal carotid artery intracranially. After operation, the bruit disappeared, the eye receded, and there remained only some visual impairment on the left and mild external rectus paresis on the left. Four days before readmission the left eye suddenly became congested and swollen. Examination showed reduced proptosis, external rectus paresis, dilated and fixed pupil, reduced corneal reflex, and reduced vision, all on the left side. The left carotid arteriogram showed bilateral filling of the middle and anterior cerebral arteries. The right carotid arteriogram showed the clamp to be closed. The middle meningeal artery was enlarged and anastomosed with the meningeal branch of the internal carotid, with some filling of the internal carotid in the parasellar region and a small amount of filling of the cavernous sinus (Fig. 11*A* and *B*).

D. By Other Communications Between Internal and External Carotid Arteries (Retia Mirabilia)

Anatomists Testut,[35] Batson,[1] and others have described, and all neurosurgeons have seen, small anomalous arteries which extend from the various branches of the meningeal arteries through the dura and anastomose with the arteries on the surface of the brain. Since the meningeal arteries in the dura are in communication with the arteries of the scalp by anastomoses through the bone, any of the branches of the external carotid artery which supplies blood to the scalp or the base of the skull could, under special circumstances, supply blood to the cerebral hemispheres.

Two such communications have been demonstrated arteriographically.

Case 14.—Direct communication between the middle meningeal artery and the middle cerebral artery.

A 33-year-old woman had sudden onset of headache, drooping of the right upper eyelid, and double vision. Arteriography showed an aneurysm of the internal carotid artery. She was treated by ligation of the internal carotid artery in the neck; and when the internal carotid artery disintegrated as the intracranial approach was being made, it was necessary to ligate the internal carotid and the posterior communicating arteries. A right common carotid arteriogram performed two months after the operation showed a considerably enlarged middle meningeal artery, which anastomosed with a branch of the orbitofrontal in the region of the Sylvan point and then supplied blood to the middle cerebral artery with resultant filling of the orbitofrontal, pre-Rolandic, Rolandic, and post-Rolandic branches (Fig. 12*A* and *B*).

Comment.—Since the internal carotid artery had previously been ligated in the neck and intracranially, the middle cerebral artery could not have been filled by way of

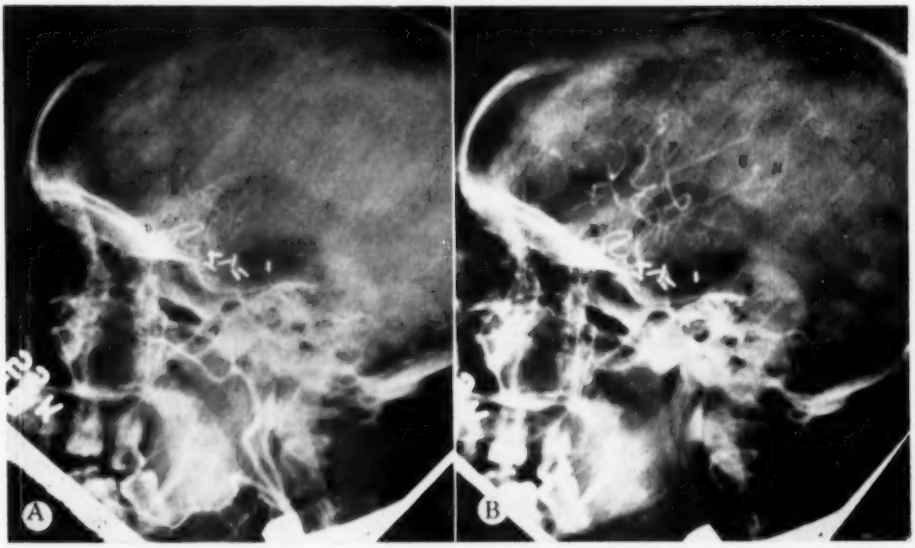


Fig. 12 (Case 14).—Direct anastomosis between middle meningeal and middle cerebral artery.

A, The film taken at one and one-half seconds (one of stereoscopic pair) shows the clamp on the internal carotid artery (*B*), the clips on the internal carotid and posterior communicating arteries (*C*), the enlarged middle meningeal artery (*D*), and orbitofrontal branches of the middle cerebral arteries (*E*).

B, the film taken at two and one-half seconds (one of stereoscopic pair) shows the middle meningeal artery (*D*) and the orbitofrontal (*E*), pre-Rolandic (*F*), Rolandic (*G*), and post-Rolandic (*H*) branches of the middle cerebral artery.

the internal carotid or by back-flow through the ophthalmic artery. In the stereoscopic and seriographic arteriograms it was possible to follow the contrast material directly from the enlarged anterior branch of the middle meningeal artery into the retia mirabilia, and thence into the orbitofrontal branch and into the middle cerebral artery itself.

Case 5.—Direct anastomoses from both occipital arteries through the bone and dura with the posterior branches of the middle cerebral artery. (This case is described earlier in this article.)

When enlarged arterial vascular channels are seen in the skull, there is a contribution from the external carotid artery to the arteriovenous angioma.

Comment

It is clear that the collateral circulation of the cerebral hemisphere is from multiple sources and is variable. The potential for collateral circulation is great, as has been demonstrated clinically in the patients who had both common and external carotid arteries ligated without complications; and as has been demonstrated anatomically by way of the circle of Willis, by the direct end-to-end anastomoses among distal branches of the anterior, middle, and posterior cerebral arteries, and by the anastomoses between the external and internal carotid arteries. In addition, the existing anastomotic vessels enlarge, as do hypoplastic arteries, in response to the differential in blood pressure between the joined arteries. Thereby the rate of cerebral blood flow is increased, since the rate of blood flow is dependent upon the pressure head and the resistance to the flow of the blood through the vessels. The important consideration is the rapidity with which this collateral circulation can be established. Kety [16] has shown that, although the brain represents but 2% of the total body weight, it normally receives 16.66% of the total output

of the blood from the heart and consumes 20% of the oxygen used by the whole body. Further, the brain cells will live only eight minutes without oxygen. Hence it is evident that the collateral circulation must be rich in order to permit sudden ligation or occlusion of a major artery to the brain; or if the potential is present, though the circulation is not immediately available, gradual occlusion is possible without complications.

Summary

1. The collateral circulation of the brain is by way of the circle of Willis, by anastomoses of the branches of the anterior, middle, and posterior cerebral arteries with each other, and by anastomoses between the external and the internal carotid artery. This has been demonstrated arteriographically in patients who had previously been treated for intracranial aneurysms and in patients with spontaneous cerebral thrombosis.

2. While the circle of Willis is the most important source of collateral circulation and its anterior part is the dominant contributor, it is extremely variable, since it is usually irregularly developed. According to Riggs, the circle of Willis is complete and conforms to the so-called normal pattern in only 18% of cases.

3. Direct anastomoses of the anterior middle and posterior cerebral arteries with each other, which were well described anatomically by vander Eecken and Adams, have been demonstrated arteriographically.

There are direct end-to-end anastomoses or smaller connecting channels as follows:

(*a*) Between the anterior and the middle cerebral arteries: the frontopolar with the orbitofrontal; the anterior, middle, and posterior internal frontal with the orbitofrontal; the posterior internal frontal with the pre-Rolandic; the paracentral with the Rolandic, and the precuneal with the post-Rolandic

(*b*) Between the anterior and posterior cerebral: the precuneal and pericallosal with the parieto-occipital

(*c*) Between the posterior cerebral and the middle cerebral: the parieto-occipital with the posterior parietal and angular; the calcarine and the posterior temporal with the posterior temporal of the middle cerebral, and the anterior temporal branches of the two arteries

(*d*) Among various branches of both anterior cerebral arteries, in addition to the anterior communicating artery

4. There are communications between the external and internal carotid arteries and their branches by way of the ophthalmic, by back-flow from the external into the internal carotid, by anastomoses between middle meningeal and the meningeal branch of the internal carotid, and via rete mirabile.

Neurological Institute, 700 West 168th St.

REFERENCES

1. Batson, O. V.: Anatomical Problems Concerned in the Study of Cerebral Blood Flow, Fed. Proc. 3:139-144, 1944.

2. Beevor, C. E.: The Cerebral Arterial Supply, Brain 30:403-425, 1907.

3. Bergstrand, H.: Olivecrona, H., and Tönnis, W.: Gefässmissbildungen und Gefässgeschwülste des Gehirns, Leipzig, VEB-Georg Thieme, 1936.

4. Brackett, C. E., Jr., and Mount, L. A.: Some Observations on Intra-Carotid Blood Pressure Made During Carotid Ligation for Intracranial Aneurysms, S. Forum (1950), pp. 344-350, 1951.

5. Cobb, S.: The Cerebral Circulation: XIII. The Question of "End-Arteries" of the Brain and the Mechanism of Infarction, Arch. Neurol. & Psychiat. 25:273-280, 1931.

6. Corday, E.; Rothenberg, S. F., and Putnam, T. J.: Cerebral Vascular Insufficiency: An Explanation of Some Types of Localized Cerebral Encephalopathy, A. M. A. Arch. Neurol. & Psychiat. 69:551-570, 1953.

7. Denny-Brown, D.: Symposium on Specific Methods of Treatment: Treatment of Recurrent Cerebrovascular Symptoms and the Question of "Vasospasm," M. Clin. North America 35:1457-1474, 1951.

8. Elschnig, A.: Die Folgen der Carotisunterbindung für das Centralgefässsystem der Retina, Med. Klin. 7:1493-1494, 1911.

9. Elschnig, A.: Über den Einfluss des Verschlusses der Arteria ophthalmica und der Carotis auf das Sehorgan, von Graefes Arch. Ophth. 39:151-177, 1893.

10. Ethelberg, S.: On Changes in Circulation Through the Anterior Cerebral Artery: A Clinico-

Angiographical Study, Acta psychiat. et neurol., Supp. 75, 1951.

11. Fay, T.: The Cerebral Vasculature: Preliminary Report of Study by Means of Roentgen Ray, J. A. M. A. 84:1727-1730, 1925.

12. Fisher, A. G. T.: A Case of Complete Absence of Both Internal Carotid Arteries, with a Preliminary Note on the Developmental History of the Srapedial Artery, J. Anat. 48:37-46, 1913.

13. Frovig, A. G.: Bilateral Obliteration of Common Carotid Artery; Thromboangitis Obliterans? A Contribution to the Clinical Study of Obliteration of the Carotids and to Elucidation of Cerebral Vascular Circulation, Acta psychiat. et neurol. scandinav., Supp. 39, 1946.

14. Heubner, J. L. O.: Zur Topographie der Ernährungsgebiete der einzelnen Hirnarterien, Centralbl. med. Wissensch. 10:817-821, 1872.

15. Jefferson, G.: Personal communication to the authors.

16. Kety, S. S.: Circulation and Metabolism of the Human Brain in Health and Disease, Am. J. Med. 8:205-217, 1950.

17. Kramer, S. P.: On the Function of the Circle of Willis, J. Exper. Med. 15:348-364, 1912.

18. Krieg, W.: Kollateralkreislaufentwicklung bei Durchblutungsstörungen des Gehirns im arteriographischen Bild: Eine pathogenetische Betrachtung, Zentralbl. Chir. 66:562, 681, 1939.

19. Lowrey, L. G.: Anomaly in the Circle of Willis, Due to Absence of the Right Internal Carotid Artery, Anat. Rec. 10:221-222, 1916.

20. Marx, F.: An Arteriographic Demonstration of Collaterals Between Internal and External Carotid Arteries, Acta radiol. 31:155-160, 1949.

21. Egas Moniz: L'Angiographie cérébrale, ses applications et résultats en anatomie, physiologie et clinique, Paris, Masson & Cie, 1934.

22. Mount, L. A., and Taveras, J. M.: A Study of the Collateral Circulation of the Brain Following Ligation of the Internal Carotid Artery, Tr. Am. Neurol. A. 78:47-49, 1953.

23. Padget, D. H.: The Circle of Willis: Its Embryology and Anatomy, in Dandy, W. E.: Intracranial Arterial Aneurysms, New York, Comstock Publishing Co., Inc., 1944, pp. 67-90.

24. Raney, R.; Raney, A. A., and Sanchez Perez, J. M.: Role of Complete Cerebral Angiography in Neurosurgery, J. Neurosurg. 6:222-237, 1949.

25. Ray, B. S.: Cerebral Arteriovenous Aneurysms, Surg. Gynec. & Obst. 73:615-648, 1941.

26. Riegner, O.: Über doppelseitiges Aneurysma der Carotis communis, durch Unterbindung beider Carotiden Geheilt, Zentralbl. Chir. 11:413-433, 1884.

27. Riggs, H. E., and Griffiths, J. O.: Anomalies of the Circle of Willis in Persons with Nervous and Mental Disorders, Arch. Neurol. & Psychiat. 39:1353-1354, 1938.

28. Rosegay, H., and Welch, W. K.: Peripheral Collateral Circulation Between Cerebral Arteries: A Demonstration by Angiography of the Meningeal Arterial Anastomoses, J. Neurosurg. 11:363-377, 1954.

29. Sachs, E., Jr.: Arteriographic Demonstration of Collateral Circulation Through Ophthalmic Artery in Internal Carotid Artery Thrombosis: Report of 2 Cases, J. Neurosurg. 11:405-409, 1954.

30. Schurr, P. H., and Wickbom, I.: Rapid Serial Angiography: Further Experience, J. Neurol. Neurosurg. & Psychiat. 15:110-118, 1952.

31. Seaman, W. B.; Page, W. R., and German, W. J.: Arteriographic Findings in Brain Arterial Occlusion, Tr. Am. Neurol. A. 74:55-60, 1949.

32. Sweet, W. H., and Bennett, H. S.: Changes in Internal Carotid Pressure During Carotid and Jugular Occlusion and Their Clinical Significance, J. Neurosurg. 5:178-195, 1948.

33. Takahashi, K.: Die percutane Arteriographie der Arteria vertebralis und ihrer Versorgungsgebiete, Arch. Psychiat. 111:373-379, 1940.

34. Taveras, J. M.; Mount, L. A., and Friedenberg, R. M.: Arteriographic Demonstration of External-Internal Carotid Anastomoses Through the Ophthalmic Arteries, Radiology 63:525-530, 1954.

35. Testut, L., and Latarjet, A.: Tratado de anatomia human, Barcelona, Salvated, S. A., 1931, Vol. 3, p. 18.

36. Torkildsen, A., and Koppang, K.: Notes on the Collateral Cerebral Circulation as Demonstrated by Carotid Angiography, J. Neurosurg. 8:269-278, 1951.

37. vander Eecken, H. M., and Adams, R. D.: The Anatomy and Functional Significance of the Meningeal Arterial Anastomoses of the Human Brain, J. Neuropath. & Exper. Neurol. 12:132-157, 1953.

38. Welch, K.; Stephens, J.; Huber, W., and Ingersoll, C.: The Collateral Circulation Following Middle Cerebral Branch Occlusion, J. Neurosurg. 12:361-368, 1955.

39. Willis, T.: Two Discourses Concerning the Soul of Brutes, in his Practice of Physick, Being the Whole Works of That Renowned and Famous Physician, Containing These Eleven Several Treatises, London, T. Dring, C. Harper, & J. Leigh, 1684, p. 154.

40. Wood, J. R.: Early History of the Operation of Ligature of the Primitive Carotid Artery, with a Report of Forty-Eight Unpublished Cases and a Summary of Forty-Four Cases, New York, H. Baillière, 1857; reprinted from New York J. Med., s. 3, 3:9-65, 1857.

Effects of Chlorpromazine on Cerebral Circulation and Electroencephalogram in Cats

DAVID H. INGVAR, M.D., Lund, Sweden, and ULF SODERBERG, M.K., Stockholm

In several recent experimental and clinical studies the action of chlorpromazine (2-chloro-10-[3-dimethylaminopropyl] phenothiazine hydrochloride) upon central nervous structures has been studied. Thus, Laborit and Huguénard [10] demonstrated its general sedative action, and Courvoisier et al.[2] reported several effects of the drug which were due to its central depressing action, e. g., its vasodilating, muscle-relaxant, and antiemetic properties. Both groups also pointed out that chlorpromazine potentiated anesthesia. Dobkin et al.,[3] furthermore, have shown that it depresses reflexes elicited from the respiratory tract. Terzian [17] and Hiebel et al.[6] studied the effects of chlorpromazine upon the EEG. They found that the drug induced a synchronized pattern with slow waves and spindles, due to its depressing action upon the reticular activating system of the brain stem. Similar results have been obtained by Turner et al.[18] and others in clinical studies.

Chlorpromazine has also been used as a muscle-relaxant in motor disorders and psychic states characterized by spasticity or tension (Lehmann and Haurahan [12] and Basmajian and Szatmari [1]). It was recently reported by Henatsch and Ingvar [5] (1956) that chlorpromazine diminishes or blocks the activity of the so-called gamma motoneurons which innervate the muscle spindles and that this effect was probably exerted through an influence upon the reticular system of the brain stem. This action of the drug may be of significance for the explanation of its effect upon the muscle tone.

The present study was carried out with a new method of recording the cerebral blood flow (Ingvar and Söderberg [8]), by which it has been demonstrated that general changes in the EEG may be accompanied by changes of the cerebral vascular resistance (Ingvar [7]; Ingvar and Söderberg [9]). It has now been found that chlorpromazine in the lightly anesthetized preparation reduces the cerebral vascular resistance and that spindles and slow waves at the same time may appear in the EEG.

Method

The method, which is described in detail elsewhere (Ingvar and Söderberg [9]), measures the outflow from the cannulated superior sagittal sinus (after elimination of diploic anastomoses) by an electric drop recorder. Preparations under pentobarbital (Nembutal) or thiopental (Penthothal) anesthesia or of the *encéphale* or *cerveau isolé* type (prepared under ether, followed by thiopental) were used. The EEG was recorded with bipolar leads from rostral parts of the brain. The blood pressure was measured in the femoral artery with an electromanometer. Chlorpromazine* was slowly administered intravenously in a 0.5% solution (usually in doses of 1 mg. per kilogram) or intra-arterially, in the carotid artery. The ear skin temperature was measured as an index of cutaneous blood flow.

Results

In the lightly anesthetized animal with intact brain stem chlorpromazine was found to reduce the cerebral vascular resistance.

Received for publication Sept. 19, 1956.

From the Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, and the Department of Physiology, University of Lund.

Aided by grants from the Swedish Medical Research Council, the fund *Therese och Johan Anderssons Minne* and from Karolinska Institutet (*Reservationsanslaget*).

*The preparation Hibernal was provided by A. B. Leo, Hälsingborg, Sweden.

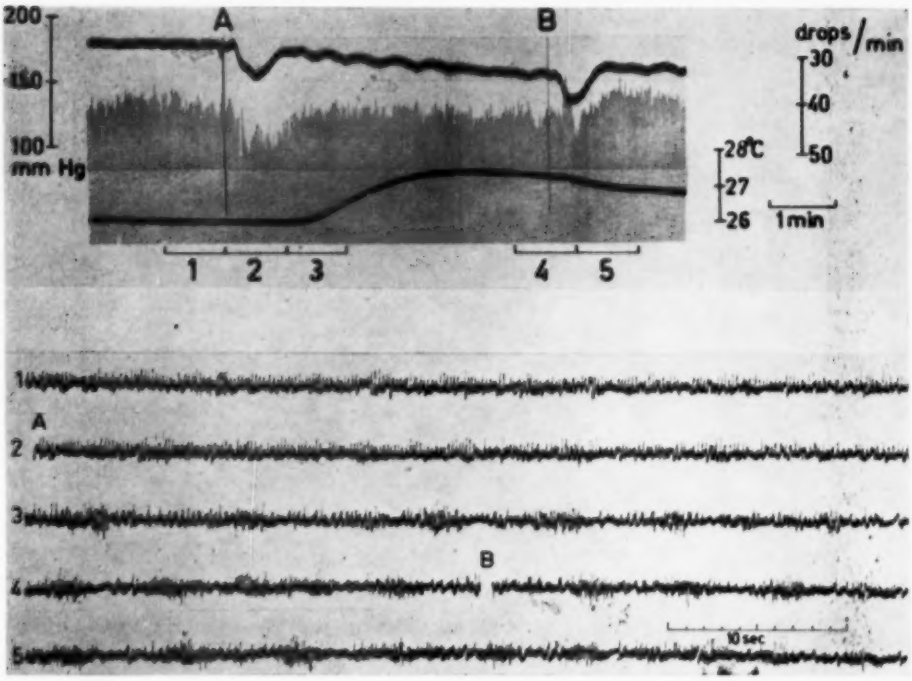


Fig. 1.—Cat, light pentobarbital (Nembutal) anesthesia. Upper diagram: blood pressure, cerebral blood flow, and ear skin temperature. Lower diagram: EEG tracing from bipolar leads on anterior suprasylvian gyrus. Tracings *1* to *5* correspond in time to periods marked below upper diagram. In record of cerebral blood flow the length of every vertical line represents the time interval between two successive blood drops from the cannulated superior sagittal sinus. A curve inversely proportional to the flow is thus obtained by joining the upper ends of the vertical lines (cf. calibration to the right). *A*, intravenous injection of 1.25 mg/kg. of chlorpromazine; *B*, intravenous injection of 3γ/kg. of epinephrine. Note increased cerebral flow immediately after the injection of chlorpromazine (*A*) in spite of transient drop in blood pressure. Ear skin temperature increases also, indicating cutaneous vasodilatation. EEG records demonstrate a change into a spindle pattern, which is uninfluenced by epinephrine (*B*).

On intravenous injection there was generally an initial phase of very marked vasodilatation in the brain, followed by a period of less pronounced dilatation. After an initial transient drop, the blood pressure was then observed to decrease substantially (Courvoisier et al.[2]). The reduced vascular resistance in the brain lasted several hours. Cerebral vasodilatation was also observed after injections in the carotid artery.

Concomitantly with the vasomotor changes there was generally a decrease of the cortical state of excitability, which in the EEG was shown by the appearance of spindles and slow waves in a synchronized pattern (Fig. 1). This confirms the findings of Terzian [17] and of Hiebel et al.[6]

In *encéphale isolé* preparations chlorpromazine induced a marked reduction of the systemic blood pressure, which made it impossible to judge whether an active change of the cerebral vascular resistance took place or not. In the EEG there was generally a depression, which most likely could be ascribed to the failure of the systemic circulation. It should, however, be pointed out that the general level of the systemic arterial pressure is, as a rule, lower in the *encéphale isolé* cats than in animals under light pentobarbital anesthesia.

The effects upon the cerebral vascular resistance and the EEG described above were not seen in *cerveau isolé* preparations

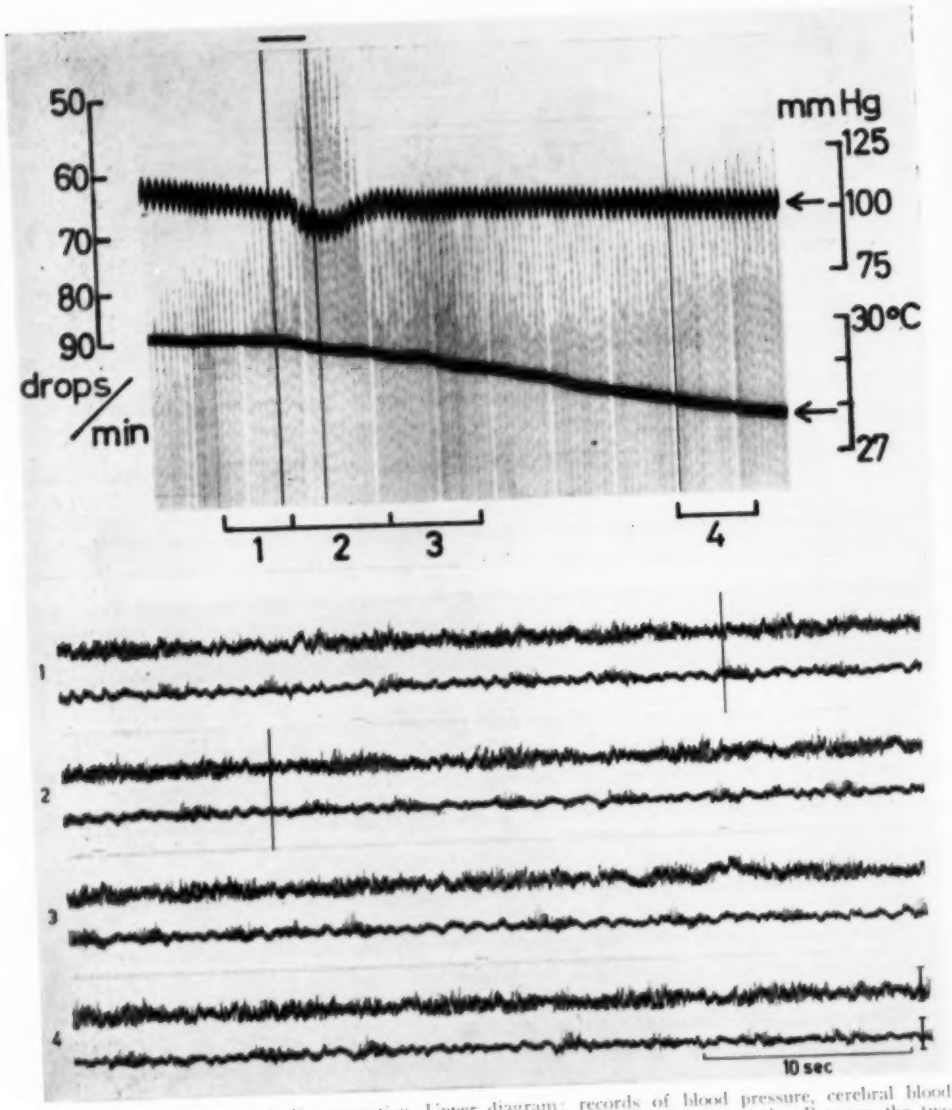


Fig. 2.—Cat, *cerveau isolé* preparation. Upper diagram: records of blood pressure, cerebral blood flow (cf. Fig. 1), and ear skin temperature. Record interrupted every 30 seconds. Between the two thick vertical lines, 1 mg/kg. of chlorpromazine was administered intravenously. Lower diagram: bipolar EEG leads from cruciate area (upper tracing) and anterior suprasylvian gyrus (lower tracing) during time periods marked in upper diagram by numerals *1* to *4*. Note decreased cerebral blood flow as a consequence of the fall in blood pressure. No effects in the EEG.

(intercollicular section) (Fig. 2) or in deeply anesthetized preparations.

In accordance with the findings of Courvoisier et al.[2] and of Foster et al.,[4] administration of epinephrine after chlorpromazine gave reduction of the blood pressure, a finding which has been interpreted to show a sympatholytic action of the drug. The effects of epinephrine upon the cerebral functions after chlorpromazine, however, requires further investigation. The action of the drug upon the cutaneous cir-

culation (measured by the ear temperature) was also in good agreement with the findings of the above-mentioned authors.

Comment

The main result of the present investigation is that chlorpromazine has been found to reduce the cerebral vascular resistance. No reduction could, however, be seen from chlorpromazine when the main part of the reticular activating system was eliminated anatomically (*cerveau isolé* preparations) or functionally (deep barbiturate anesthesia). Thus, the effect of chlorpromazine may be exerted upon those structures in the brain stem which influence the cerebral circulation (Ingvar[7]) and which form a part of the reticular activating system (Moruzzi and Magoun[13]). Whether changes in cerebral blood flow are elicited by vasomotor nerves or humoral systems or whether they are a passive consequence of altered electrical activity can, however, not be stated here. In this connection, the investigation of Foster et al.[4] in man may be recalled. They concluded that chlorpromazine induced vasodilatation in an extremity mainly as a result of its central action, although the local effects of the drug in the peripheral vessels were substantial. The peripheral and central actions of chlorpromazine upon muscle blood flow have also recently been studied by Söderberg.[15]

Chlorpromazine, which, like the barbiturates, has a sedative action, would seem to differ from these drugs. Smaller doses of barbiturates, sufficient to evoke barbiturate spindles in the EEG, would not induce such marked changes in the cerebral vascular resistance as chlorpromazine did, although both types of drugs lowered the blood pressure. It may in general be said that the states of decreased cortical excitability and reduced cerebral vascular resistance after chlorpromazine are more similar to those in ordinary sleep. In sleep there is—in contrast to the anesthetized state—a slight reduction of the blood pressure together with a significant lowering of the cerebral vascular resistance (Sokoloff[16]). It should also be pointed out that the cerebral vascular state after chlorpromazine, with its depression of the EEG, differs principally from the state of cortical "arousal," in which there is also a decrease of the cerebral vascular resistance concomitant with desynchronization of the EEG (Ingvar[7]; Ingvar and Söderberg[8,9]).

In view of the reported relation between cerebral vasomotor tone and psychic disease (Shenkin et al.[14]) and of the wide use of chlorpromazine in psychic disorders, the present new information on the drug would seem significant.

It may be added that in the doses employed (1 mg. per kilogram) chlorpromazine seems to have a much more dramatic action upon, e. g., the muscle tone (Henatsch and Ingvar[5]) than upon the EEG. Such a dose may completely eliminate gamma motor activity, while the effects upon the EEG are, although evident, rather small. This observation would justify the assumption that the reticular activating system may be regarded as consisting of several functional units upon which chlorpromazine exerts different effects (Hiebel et al.[6]).

Summary

Chlorpromazine reduces the cerebral vascular resistance in cats with an intact and functioning brain stem. Concomitantly with the vasodilatation, spindles and slow waves may appear in the electroencephalogram.

Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm (Dr. Söderberg).

REFERENCES

1. Basmajian, J. V., and Szatmari, A.: Effect of Largactil (Chlorpromazine) on Human Spasticity and Electromyogram, A. M. A. Arch. Neurol. & Psychiat. 73:224-231, 1955.

2. Courvoisier, S.; Fournel, J.; Ducrot, R.; Kolsky, M., and Koetschet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3(diméthylamino-3' propyl)-10 phénothiazine (4.560 R. P.), Arch. internat. pharmacodyn. 92:305-361, 1953.

3. Dobkin, A. B.; Gilbert, R. G. B., and Lamoureux, L.: Physiological Effects of Chlorpromazine, Anæsthesia 9:157-174, 1954.

4. Foster, C. A.; O'Mullane, E. J.; Gaskell, P., and Churchill-Davidson, H. C.: Chlorpromazine: A Study of Its Action on the Circulation in Man, Lancet 2:614-617, 1954.

5. Henatsch, H.-D., and Ingvar, D. H.: Chlorpromazin und Spastizität: Eine experimentelle elektrophysiologische Untersuchung, Arch. Psychiat. 195:FF-93, 1956.

6. Hiebel, G.; Bonvallet, M., and Dell, P.: Action de la chlorpromazine ("largactil," 4560 RP) au niveau du système nerveux central, Semaine hôp. Paris 30:2346-2353, 1954.

7. Ingvar, D. H.: Extraneuronal Influences upon the Electrical Activity of Isolated Cortex Following Stimulation of the Reticular Activating System, Acta physiol. scandinav. 33:169-193, 1955.

8. Ingvar, D. H., and Söderberg, U.: A direct Method for the Measurement of Cerebral Blood Flow, Nature, London 177:339-340, 1956.

9. Ingvar, D. H., and Söderberg, U.: A New Method for Recording Cerebral Blood Flow in the Relation to the Electroencephalogram, Electroencephalog. & Clin. Neurophysiol. 8:403-412, 1956.

10. Laborit, H., and Huguénard, P.: L'hibernation artificielle par moyens pharmacodynamiques et physiques en chirurgie, Presse méd. 59:1329, 1951; cited by Laborit, Huguénard, et al.[11]

11. Laborit, H.; Huguénard, P., and others: Pratique de l'hibernothérapie en médecine et en chirurgie Paris, Masson & Cie, 1953.

12. Lehmann, H. E., and Haurahan, G. E.: Chlorpromazine: New Inhibiting Agent for Psychomotor Excitement and Manic States, A. M. A. Arch. Neurol. & Psychiat. 71:227-237, 1954.

13. Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. 1:455-473, 1949.

14. Shenkin, H. A.; Woodford, R. B.; Freyhan, F. A., and Kety, S. S.: Effects of Frontal Lobotomy on Cerebral Blood Flow and Metabolism, A. Res. Nerv. & Ment. Dis., Proc. (1947) 27:823-831, 1948.

15. Söderberg, U.: Effects of Chlorpromazine on Muscle Blood Flow, to be published.

16. Sokoloff, P.: Relation of Cerebral Circulation and Metabolism to Mental Activity, Neurochemistry, edited by S. R. Korey and J. I. Nurnberger, New York, 1956.

17. Terzian, H.: Studio elettroencephalographico dell'azione centrale del largactil (4560 RP), Rass. neurol. veget. 9:211-215, 1952.

18. Turner, M.; Bérard, E.; Turner, N., and Franco, N.: Modifications électro-encéphalographiques, électro-dermographiques et électromyographiques provoquées par la chlorpromazine chez l'homme, Electroencephalog. & Clin. Neurophysiol. 8:25-34, 1956.

Experimentally Induced Epilepsy in the Cat with Injury of Cornu Ammonis

JOHN D. GREEN, D.M. (Oxon.); CARMINE D. CLEMENTE, Ph.D., and JACOB de GROOT, M.D., Los Angeles

Seizures originating in the temporal lobe have been associated with the pathological findings of scars in the cornu ammonis (hippocampus) since 1825, when, according to Gastaut,[1] Bouchet and Cazauvielh[2] first noticed macroscopically detectable lesions in this area. It has been argued in the past (*a*) that such lesions may be secondary to the epileptiform attacks, (*b*) that the hippocampus is not concerned with motor activities and, consequently, is not likely to be concerned in motor fits, and (*c*) that similar lesions may be found in nonepileptic subjects. Nevertheless, seizure discharges were evoked upon stimulation of the hippocampus by Kaada,[3] Green and Morin,[4] and Morin and Green[5]; and motor fits have been seen by Kaada, Jansen, and Andersen,[6] Green and Shimamoto,[7] and others. Such discharges, spreading to the rest of the brain apparently via the temporal lobe more readily than via the fornix,[7,8] have indicated that seizure discharges elicited from the hippocampus affects the cortex more readily than seizure discharges induced by stimulation of the amygdala. Finally, some authors have found damage to the hippocampus in an extraordinarily high percentage of cases of temporal lobe epilepsy.[9-11]

In the course of an investigation on the effects of temporal lobe lesions, 15 cats out of a total of 82 developed motor fits, and 8 additional animals showed symptoms possibly due to sensory seizures. This paper is concerned with these 23 cats.

Received for publication Sept. 28, 1956.

Present Address: University of Leiden, Netherlands (Dr. de Groot).

Aided in part by the U. S. Public Health Service Grant No. B610.

From the Department of Anatomy, University of California at Los Angeles, and Veterans' Administration Center.

Materials and Methods

Electrolytic lesions were made bilaterally with the Horsley-Clarke stereotaxic apparatus and a D. C. lesion maker. Surgical lesions were made by incision or aspiration. The animals were all adult cats in healthy condition at the time of operation. They were observed preoperatively for at least one week and on the average of two months postoperatively, some considerably longer (up to six months) and others for less time, especially in the cases of death in status epilepticus. Behavior was recorded cinematographically, and some of the animals are illustrated in a film produced at the University of California.

Results

In the majority of cases the postoperative recovery was uneventful during the first week. Behavioral and physiological changes other than seizures have been described elsewhere.[12] This paper deals only with the epileptiform condition and the associated pathological findings in a group of 23 adult cats. The temporal lobe epilepsy occurred chiefly in the first two postoperative weeks. Subsequently the seizures abated but in one instance were seen to recur after six weeks.

Characteristics of Seizures.—The characteristic seizure sequence was often arrested at one or another stage but was otherwise very constant. At times seizures could be triggered by repeated click stimulation, by flashing light from a stroboscope lamp, or by tactile stimulation (repeated stroking). At other times it was impossible to trigger fits, and it was felt that the state of the animal, or possibly the element of surprise, was important. The cats showed "prodromal" activity: sudden turning of the head

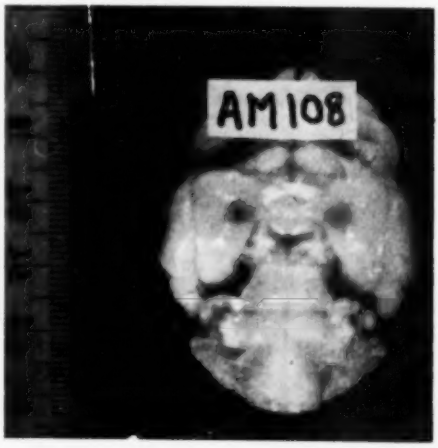
to the right or left, fixed staring, crouching, or peculiar arrested postures. Sometimes, more organized prodromal signs were observed, such as pouncing on the floor of the cage or walls or patting the air as if with a toy. Pupillary dilatation was usually the first sign of an approaching fit and was followed by salivation, gagging, and clonic facial twitching, in that order. The clonic facial twitching was then succeeded by a march of movement from the face to the neck, forelimbs, trunk, and hindlimbs. A tonic phase was seen occasionally, but the movements were almost always clonic.

Some animals showed curious behavior at the onset of the seizure. One crouched with fur erect and ears laid back. When touched, it leaped about 3 ft. and again assumed the same position. This was repeated a number of times without a full motor fit ensuing. The leaps appeared to be well executed, and the animal did not collide with adjacent objects. Another cat seemed to display fear of a clicker as the seizure began, although indifferent to it between fits. Between seizures many animals showed a behavior pattern resembling fear. They would snarl at the investigator when the cage door was opened and the hand inserted. They would run away from other cats or snarl and strike when held in front of the cages of other animals. This seemed progressive, for if the cat was presented to a series of animals in this way, its behavior became more and more adverse. Three cats seemed to become hyperesthesic when stroked, and this also was followed by apparent accentuation of fear of other cats and of the investigator. If such behavior patterns may be considered as sensory seizures, then we may add another 8 cats, making a total of 23 with seizures out of the 82. The seizures seen occurred chiefly during the first three postoperative weeks, commonly starting on the second or third day. In one animal seizures recurred after an interval of six weeks.

Pathological Findings.—Among the 82 animals studied, there were 47 cases in which the amygdala was involved and 17 cases in which the piriform cortex was involved. In 25 cases the hippocampus was damaged; however, among all of the 15 cats that developed motor seizures there was extensive hippocampal involvement. There was also minor hippocampal involvement in all cats (eight) with signs suggestive of sensory seizures. Thus, two animals with hippocampal involvement showed no abnormalities whatever, but their lesions were minimal.

Of the 15 cats with motor fits, 11 showed signs suggestive of "sensory fits." The remaining four either died very soon postoperatively or had very extensive lesions. In four of the cats which had motor fits there was no apparent involvement of any structure other than the hippocampus. In these animals only the dorsal hippocampus was destroyed, so that the temporal lobe was not involved in any way. In seven cats there was very extensive hippocampal destruction. These animals are particularly interesting because the primary lesion was not in the hippocampus itself but in the amygdala and periamygdaloid cortex (Text-Figure). Of these seven cats, six had extensive bilateral injury to the hippocampus. Four examples are illustrated in Plate 1 (at 9, 40, 42, and 60 days postoperatively).

Ventral view of the brain of a cat killed nine days after the electrolytic lesions were made. This animal had grand mal seizures, commencing on the fourth postoperative day. Note the secondary hippocampal destruction in this animal in the Plate illustrations (9 *D*).



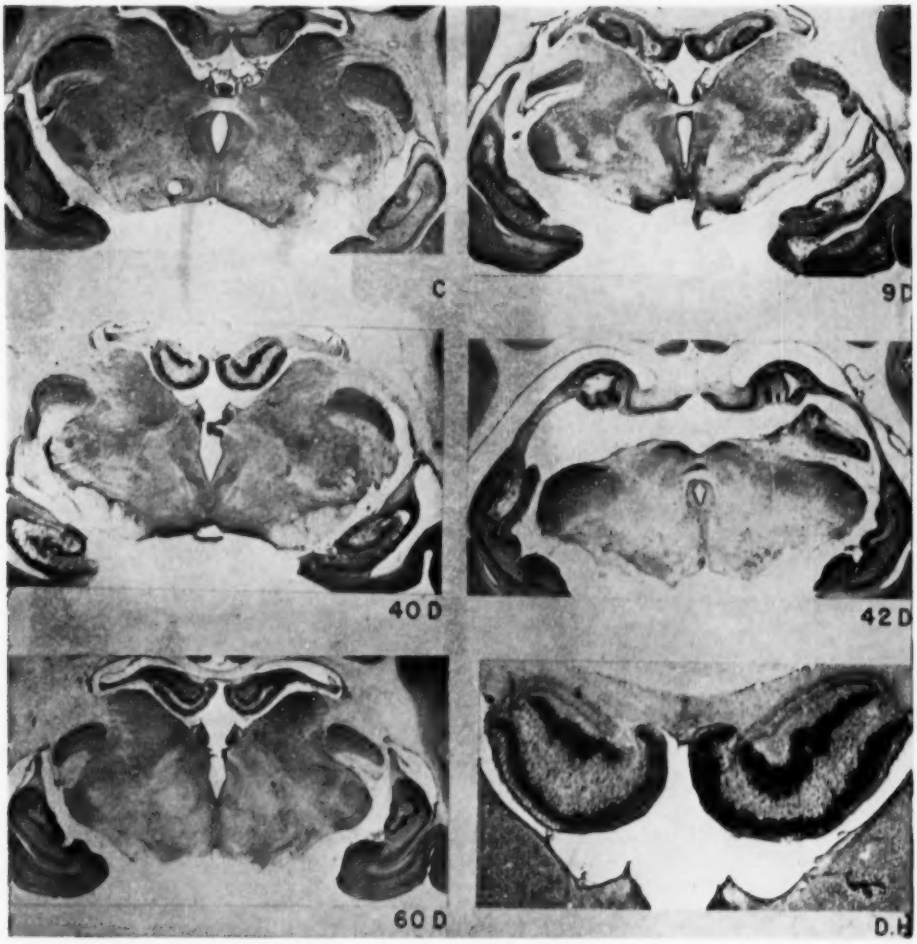


Plate 1.—These figures show cross sections of the brain stem and hippocampus of four animals which had seizures and which lived for 9, 40, 42, and 60 days after the production of the lesions. In the upper left corner is a similar cross section from a control (*C*) animal, not operated on, and in the lower right corner is a higher magnification of the dorsal hippocampus (*D. H.*) from the 40-day specimen. Thionine stain.

The hippocampi of the same animals are shown in Plate 2 at higher magnification and an example in which there was unilateral destruction only (at 177 days). The latter animal did not have motor fits. The injury strongly suggests vascular damage to the hippocampus. There are extensive cell death, scarring, gliosis, neuronophagia, and loss of normal cell pattern, followed by partial recovery, in which, however, the hilus of the gyrus dentatus commonly remained shrunken and scarred and the cell layers showed a wavy, irregular outline.

The hippocampus receives its blood supply from the anterior choroidal and the posterior cerebral arteries. The vessels lie in the groove at the edge of the gyrus dentatus and are seen well in the last figure of Plate 2. Vessels pass into the hippocampus through a pial cleft, and the entering vessels are illustrated in the same figure and in many of the others. They do not

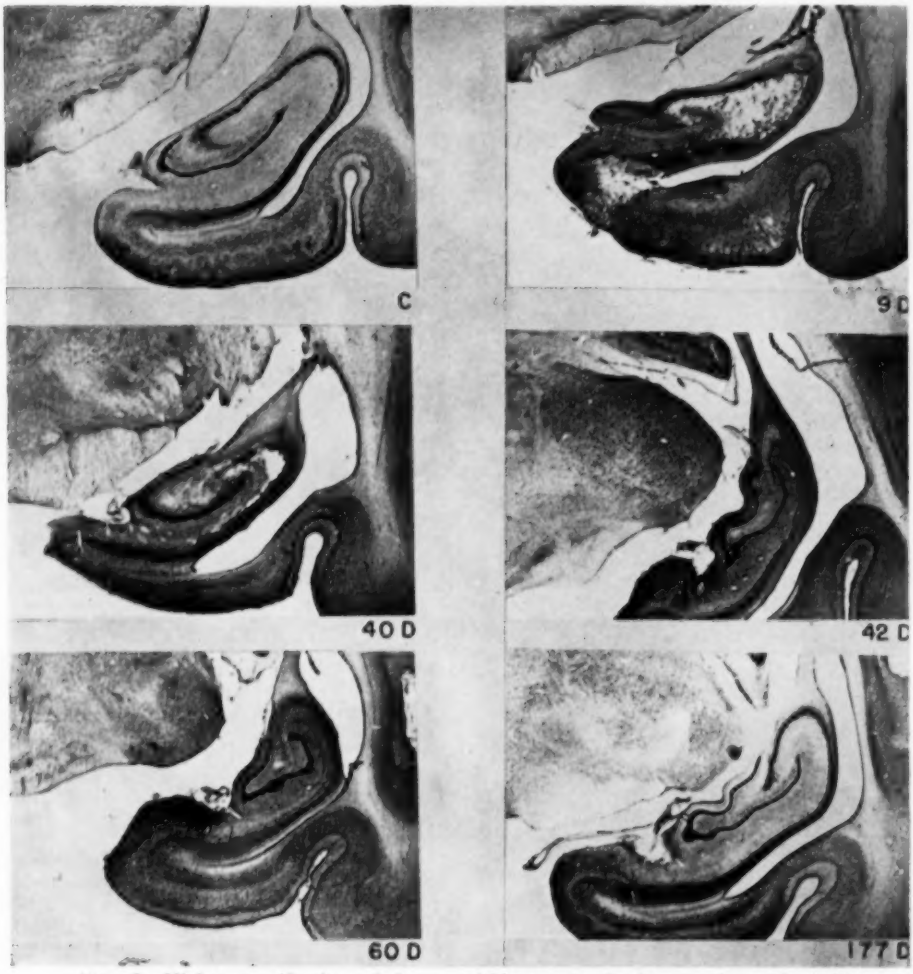


Plate 2.—Higher magnifications of the ventral hippocampus in the same four animals illustrated in Plate 1 (9, 40, 42, and 60 days), in addition to another cat, which lived 177 days. Note the hippocampal involvement in each case, as compared with the control (C) (upper left).

appear occluded in most cases, and the original injury probably caused only temporary occlusion. Consequently, the effects seen are presumably ischemic rather than true infarction, and it is probable that the hippocampus was damaged rather than totally destroyed.

Comment

The close similarity between the hippocampal scars in our cats and those found in human cases of temporal lobe epilepsy is striking. It has long been known that the hippocampus has a precarious blood supply and is easily damaged by anoxemia, carbon monoxide, and poisons.[13-15] The choroidal fissure lies close to the edge of the sella turcica and tentorium, and it is easy to imagine compression of the hippocampal vessels in the choroidal fissure against this rigid edge. The hippocampus is more easily stimulated than other cerebral areas in electroshock,[16] and generalized electrical discharges in the cerebral hemisphere may be

induced by light mechanical stimulation of the hippocampus, as well as by electrical stimulation.[7]

It is clear that seizure discharges may originate in almost any area of central gray matter.[17] However, a distinction may perhaps be made between seizure discharges and clinical seizures. The high incidence of hippocampal involvement in our experimental animal series and in patients with temporal lobe epilepsy is striking enough to suggest that there may be a common factor, and that involvement of other structures besides the hippocampus may not be necessary. It would, indeed, be rash to suggest that all temporal lobe seizures result from hippocampal injury alone.

Summary

Motor seizures were seen in 15 of 82 animals with lesions in the temporal lobe and hippocampus. Signs suggestive of sensory seizures were seen in eight more. All 23 had involvement of the hippocampus. Two animals with minor hippocampal involvement showed no abnormal signs. Seizures were not seen when the hippocampus is not involved.

General hippocampal injury may result from injuries elsewhere in the temporal lobe.

The pathology of the hippocampal lesions in our animals resembles that in humans with sclerosis of the cornu ammonis.

Department of Anatomy, University of California School of Medicine at Los Angeles (Dr. Clemente).

REFERENCES

1. Gastaut, H.: État actuel des connaissances sur l'anatomie pathologique des épilepsies, in Colloque sur les problèmes d'anatomie normale et pathologique posés par les décharges épileptiques (Marseille), Bruxelles, Les Editions Acta Medica Belgica, 1954, pp. 5-20.

2. Bouchet and Cazauvielh: De l'épilepsie considerée dans ses rapports avec l'aliénation mentale, Arch. gén. méd. 9:510-542, 1825; cited by Gastaut.[1]

3. Kaada, B. R.: Somato-Motor, Autonomic and Electrocorticographic Responses to Electrical Stimulation of "Rhinencephalic" and Other Structures in Primates, Cat and Dog, Acta physiol. scandinav. (Supp. 83) 24:1-285, 1951.

4. Green, J. D., and Morin, F.: Hypothalamic Electrical Activity and Hypothalamocortical Relationships, Am. J. Physiol. 172:175-186, 1953.

5. Morin, F., and Green, J. D.: Diffuse Afterdischarges Following Stimulation of the Fimbria Hippocampi, Am. J. Physiol. 175:251-257, 1953.

6. Kaada, B. R.; Jansen, J., Jr., and Andersen, P.: Stimulation of the Hippocampus and Medial Cortical Areas in Unanesthetized Cats, Neurology 3:844-857, 1953.

7. Green, J. D., and Shimamoto, T.: Hippocampal Seizures and Their Propagation, A. M. A. Arch. Neurol. & Psychiat. 70:687-702, 1953.

8. Arana-Iñiguez, R.; Reis, D. J.; Naquet, R., and Magoun, H. W.: Propagation of Amygdaloid Seizures, Acta neurol. latinoam. 1:109-122, 1955.

9. Stauder, K. H.: Epilepsie und Schläfenlappen, Arch. Psychiat. 104:181-212, 1936.

10. Velasco, O. P.: Contribuição anátomo-clínica às atuais concepções sôbre a epilepsia, Arq. neuro-psyquiat. 8:301-334, 1950.

11. Sano, K., and Malamud, N.: Clinical Significance of Sclerosis of the Cornu Ammonis, A. M. A. Arch. Neurol. & Psychiat. 70:40-53, 1953.

12. Green, J. D.; Clemente, C. D., and de Groot, J., In preparation.

13. Meyer, A.: Über die Wirkung der Kohlenoxydvergiftung auf das Zentralnervensystem, Ztschr. ges. Neurol. u. Psychiat. 100:201-247, 1926.

14. Meyer, A.: Lésions observées sur les pièces opératoires prélevées chez des épileptiques temporaux, in colloque sur les problèmes d'anatomie normale et pathologique posés par les décharges épileptiques (Marseille), Bruxelles, Les Editions Acta Medica Belgica, 1954, pp. 21-42.

15. Earle, K. M.; Baldwin, M., and Penfield, W.: Incisural Sclerosis and Temporal Lobe Seizures Produced by Hippocampal Herniation at Birth, A. M. A. Arch. Neurol. & Psychiat. 69:27-42, 1953.

16. Jung, R.: Hirnelektrische Untersuchungen über den Elektrokrampf: Die Erregungsabläufe in corticalen und subcorticalen Hirnregionen bei Katze und Hund, Arch. Psychiat. 183:206-244, 1949.

17. Moruzzi, G.: L'épilepsie expérimentale, Paris, Librairie Scientifique Hermann & Cie, 1950.

Alterations in Mental Function and Paroxysmal Cerebral Activity

KENNETH A. KOOI, M.D., and H. BIRNET HOVEY, Ph.D., Salt Lake City

We have previously reported a study in which we found that certain kinds of "non-answer" responses (NR's) to intelligence test items occurred to a significantly greater extent among a group of epileptics than among a group having organic brain impairment but without known seizures, and a psychiatric group, respectively.[2] Patients with paroxysmal electroencephalographic abnormality, regardless of diagnosis, also were found to demonstrate NR's significantly more frequently than those without such abnormality. NR's might be categorized as temporary losses of goal idea, or what would appear to be transient inattention, preoccupation, or internal distraction. The temporary loss of goal idea was indicated by a direct admission of confusion, request for repetition of the test instructions, a comment or criticism about the test item, a response to part of the question, or verbalization of merely a simple association.

As a result of these findings, our belief was that NR's occur concomitantly with paroxysmal electrical activity. The present study attempts to test this hypothesis and to evaluate other preliminary observations which suggested that "don't-know" responses, requests for repetition of questions, and zero-quality answers, as well as NR's, are associated with burst activity. In addition, the investigation was designed to determine the effect of the test procedure on the electroencephalographically recorded paroxysmal activity.

Received for publication July 11, 1956.

Mr. Charles D. Kroksh helped in setting up the electronic voice recorder.

From the Neurology and Clinical Psychology Services, Veterans' Administration Hospital, Fort Douglas Station, and the Neurology Section, Department of Psychiatry, University of Utah College of Medicine.

Procedure

Subjects for study consisted of 21 patients who had previously shown paroxysmal activity in EEG recordings. All had received the diagnosis of epilepsy except for one patient with periodic headaches (No. 18). The age, sex, seizure type, presumptive etiology, and significant EEG findings of each patient are shown in Table 1. Psychological tests were administered while EEG recordings were being made. Also, electronic voice records were made on the EEG tape to indicate when questions and responses were occurring. This was effected by recording the output of a crystal microphone relayed through a Grass balance-demodulator unit with the appropriate auxiliary amplification. Control EEG recordings, two minutes with eyes open and two minutes with eyes closed, were made immediately before and after psychological testing.

The Comprehension and Similarities subtests of the Wechsler Adult Intelligence Scale[10] were administered while the subject's eyes were closed. These same subtests of the Wechsler-Bellevue Intelligence Scale, Form II,[9] were administered but with eyes open. Also, with eyes open, the Picture-Completion subtests of both scales and the Digit-Symbol subtest of the Wechsler Adult Intelligence Scale were administered. The psychological test protocols were reviewed, and each response was classified as an NR, a "don't-know" response, a request for repetition of the question, or a noncredit- or a credit-score answer. A noncredit-, or zero-, score answer is one that is not adequate enough to receive a credit score, e. g., saying "holler fire" when asked what to do if one were in a movie and the first to see smoke and fire; saying that alcohol and wood are both "tree products" when more precise similarities are in order, or mentioning a relatively inconsequential missing part for a Picture-Completion item.

The EEG records were inspected, and the time required for the question, the question-to-answer period, the answer, and the interval to the next question were tabulated for each psychological

TABLE 1.—*Classification of Patients*

Patient	Age, Yr.	Sex	Seizure Type	Presumptive Etiology	EEG Findings
1	32	M	Grand mal, psychomotor	Idiopathic	Bilaterally synchronous 5-6 p.s. bursts
2	33	M	Grand mal	Post-traumatic	Shifting bitemporal spikes
3	37	M	Psychomotor and focal, right face, arm, and leg	Brain tumor	3-5 p.s. bursts, left temporal region
4	70	F	Grand mal	Post-traumatic	Focal mixed, slow, and sharp wave bursts, left temporal region
5	36	M	Grand mal, psychomotor	Idiopathic	Mixed slow and sharp wave bursts, right temporal region
6	41	M	Grand mal, petit mal	Idiopathic	Bilaterally synchronous 3-5 p.s. spike-and-wave bursts
7	16	M	Grand mal, Jacksonian, right face, neck, and arm	Post-traumatic	Continuous shifting mixed sharp and slow wave bursts, left hemisphere
8	26	M	Grand mal, petit mal	Idiopathic	Bilaterally synchronous 3 p.s. spike-and-wave bursts
9	30	M	Grand mal	Post-traumatic	Focal mixed slow and sharp wave bursts, left parietotemporal region
10	36	M	Grand mal	Idiopathic	Bilaterally synchronous 3-5 p.s. spike-and-wave bursts
11	27	M	Grand mal	Idiopathic	Bilaterally synchronous 3 and 4-7 p.s. bursts
12	26	M	Grand mal	Idiopathic	Bilaterally synchronous 2-3 p.s. wave and spike-and-wave bursts
13	16	M	Grand mal, petit mal	Idiopathic	Bilaterally synchronous 3 p.s. spike-and-wave bursts
14	26	M	Grand mal	Idiopathic	Bilaterally synchronous 3 p.s. spike-and-wave bursts
15	34	M	Grand mal	Idiopathic	Bilaterally synchronous and shifting 2-3 p.s. bursts
16	41	M	Grand mal	Idiopathic	Prefrontal 5-6 p.s. bursts
17	18	F	Grand mal	Idiopathic	Bilaterally synchronous 3 p.s. spike-and-wave bursts
18	35	M	None	—	Bilaterally synchronous and shifting 3 and 4-7 p.s. bursts
19	38	M	Grand mal, myoclonic, akinetic	Post-traumatic	Bilaterally synchronous 3-4 p.s. spike-and-wave bursts
20	62	M	Grand mal	Post-traumatic	Mixed slow and sharp wave bursts with shifting emphasis, left and right frontal regions
21	58	M	Grand mal, psychomotor	Idiopathic	Shifting bitemporal spikes

test item. The time that bursts were observed was estimated to the nearest second during the control runs and during the four periods described for each item. Bursts lasting less than one second were all recorded as 0.5 second in duration. The percentage of time that bursts were occurring was then calculated for the control and test periods.

Any test response given in association with a clinical seizure was not included in the tabulations.

Results

The following examples are illustrative of NR's. A college graduate started out by satisfactorily indicating essential missing parts in the Picture-Completion test, when after a pause he asked, "Do you want to know what is superfluous?" and then, without any comment from the examiner, resumed giving correct answers. Another subject, while examining the card showing a rooster without a spur on one leg, commented only on the rooster's wing, and spontaneously resumed noting missing parts for subsequent pictures. One subject asked, "What about it?" just after starting this test. Upon reaching the mountain-lake item in the Similarities subtest, one subject said "Rivers" as though free-associating (Fig. 1). When about two-thirds through this test, one said, "I've lost out. Don't know what I'm supposed to say on that" (Fig. 2). To the item, "Why should we keep away from bad company?" one said, as though merely commenting, "No interest in associating with them." Each of these examples was associated with at least five seconds of focal or generalized burst activity. Figures 1 and 2 exemplify recordings of psychological testing on the EEG record, including NR's.

An association between the NR and burst activity during some part of the question-through-response period was noted in two-thirds of 87 responses of this type (Table 2). This relationship was greater than for any other type of response. Thus, although our main hypothesis as originally conceived was not supported by the data, a relationship was evident. There was, of course, a possibility that the greater association of bursts with NR's was due to subjects taking slight-

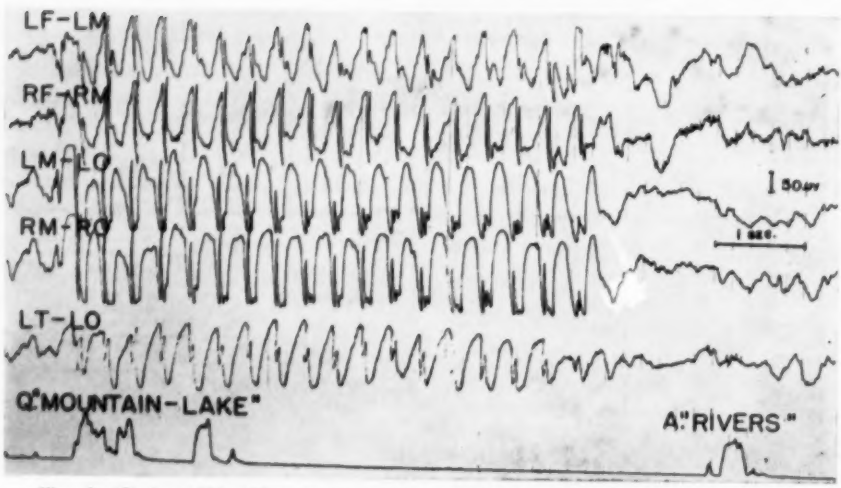


Fig. 1 (Patient 13).—Nonanswer response (NR) in association with bilaterally synchronous 3-per-second spike-and-wave discharge. Simultaneous voice record, bottom line. In this, and in subsequent figures, the leads are designated as follows: *F*, frontal; *M*, motor; *T*, temporal; *AT*, anterior temporal; *O*, occipital; *V*, vertex; *L*, left; *R*, right.

Fig. 2 (Patient 3).—Nonanswer responses (NR's) and increased response time with concomitant left temporal paroxysmal activity. After cessation of the paroxysmal discharge, the patient responds with a zero-quality answer.

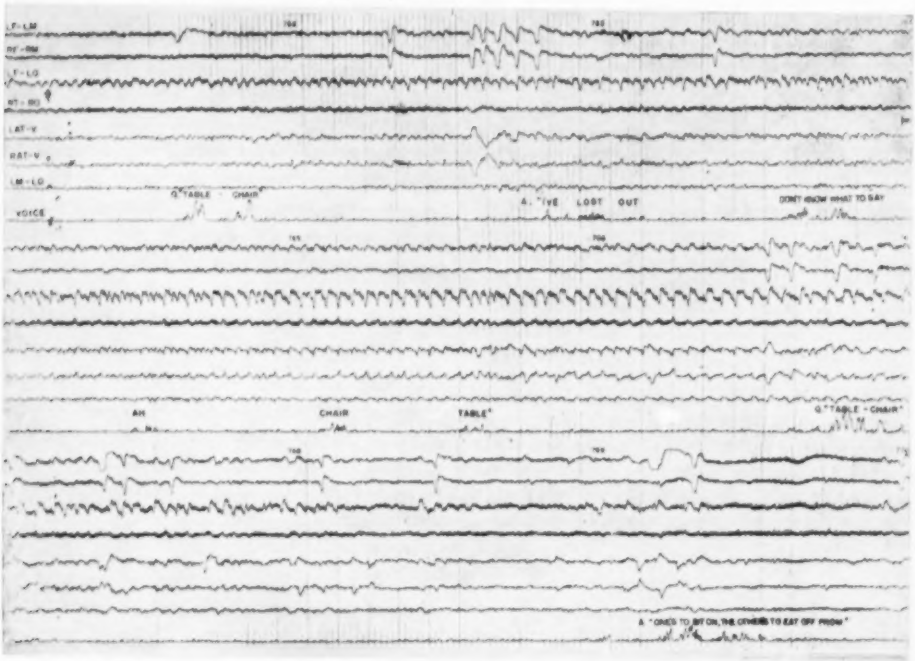


TABLE 2.—*Relation of Bursts to Type of Test Response*

Type of Response	Total Items	Percentage of Total Items with Bursts	Percentage of Time Bursts Occurred
Nonanswer	87	66.7	30.8
Don't-know	168	35.8	15.2
Repetition of question	19	26.3	19.9
Zero-score answers	412	24.3	3.8
Credit-score answers	783	14.4	3.6

ly longer when ultimately responding with NR's. That this alone was responsible for the frequent association of NR's and bursts was negated by the computation of the percentage of time that bursts occurred with each type of response. Burst activity was eight to nine times greater with NR's than with answers.

Table 2 reveals that "don't-know" responses and requests for repetition of the question are more frequently associated with burst activity than are answers. However, zero-score answers showed essentially the same association with bursts as did credit-score answers (last column of Table 2). The increased percentage of items associated with bursts in this instance can be accounted for by the longer time spent with these questions.

Since NR's were too infrequent in most cases for applying tests of significance for individual subjects, and since "don't-know" responses were often associated with bursts, NR's were combined with "don't-know" responses into one category, for comparison with answers as another category. These two categories were compared for amount of burst activity associated with each, during question-through-response periods. The χ^2 test * surpassed the 0.01 level of significance in four cases and failed to do so in eight cases, but the relationships were all in the same direction. This test could not be applied to the remaining nine cases because there was too little burst activity, especially during question-through-response periods. When the 12 χ^2 values were rank-ordered and plotted against rank-orders for burst activity, the correlation surpassed the 0.01 level ($\rho=0.89$). Thus, an important factor in the computation of the statistical significance of the relationship between bursts and NR's and "don't-know" responses in any given patient was the over-all incidence of bursts.

Not only were there qualitative differences in the type of response, but response time was also often noted to be prolonged if either focal or generalized bursts were present. The percentage of time that bursts were showing during the question-to-response interval, and the length of this interval, were plotted. For six subjects the 0.01 level was surpassed when the χ^2 test was applied. The χ^2 value failed to reach even the 0.05 level for the seventh subject. This appeared to be related to this subject's proclivity for quickly saying "don't-know," when burst activity happened to be going on. Tests for significance were not applicable for the remaining subjects because of the small number of bursts during reaction periods.

In two subjects (Nos. 7 and 13), a total of 11 seizures happened to occur during the question-through-response periods. These were Jacksonian seizures involving the right side of the face and right arm in one subject and petit mal seizures in the other. The responses were not included in the tabulations. In only one instance was a satisfactory answer given (Fig. 3), and this was when a petit mal attack occurred while the question was being asked. After the attack ceased, the patient answered the question satisfactorily without its having to be repeated. In the other 10 instances, there were 4 NR's, 3 "don't-know" responses, 2 requests for repetition of the question, and 1 zero-quality answer.

In one patient (No. 7) continuous shifting, slow and sharp wave bursts were noted over the left hemisphere. This patient gave the greatest number of NR's, and it may be assumed that the paroxysmal activity was exerting an almost constant deleterious effect upon mental function. In the other patients

* The Yates correction for sample size was used in all χ^2 tests.

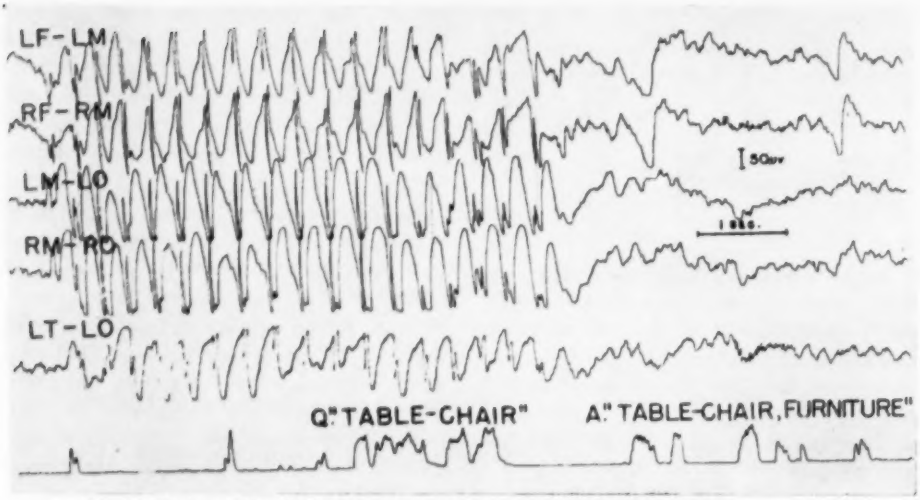


Fig. 3 (Patient 13).—Satisfactory answer to a question falling within a generalized 3-per-second spike-and-wave burst. The patient repeats the question prior to giving the answer.

with intermittent bursts the disturbances of mental function were also episodic, the frequency of NR's paralleling the incidence of paroxysmal activity. A rank-order correlation between proportion of burst activity and frequency of NR's surpassed the 0.01 level of significance for the 21 cases ($\rho = 0.67$).

Except for two patients (Nos. 3 and 20) with demonstrated organic brain damage, test performance during periods free of paroxysmal activity was within or above the normal range.

The relationship between the burst activity and ability to respond varied from case to case. In two patients (Nos. 3 and 7) responses were sometimes given during continuous focal paroxysmal activity (Fig. 2). Only one patient (No. 13) demonstrated extended 3-per-second generalized spike-and-wave bursts. These were associated with staring, rhythmical twitching of the eyelids and loss of neck tone. This patient did not respond to any question asked during a burst until after the paroxysmal activity subsided (Figs. 1 and 3). In another unusual case (No. 15) burst activity repetitiously began to increase in amplitude immediately prior to the response and remained throughout the entire response period (Fig. 4).

The loss of higher integrative mental processes, but with the retention of both memory and motor functions during paroxysmal cerebral activity, was brought out impressively by one subject. During one phase of the test, while single bilaterally synchronous spike-and-wave discharges were occurring up to 15 every 10 seconds, he was unable to answer the simplest questions, yet was able to repeat the questions accurately. Later, when the record was free of bursts, these same questions were readily answered correctly.

In eight patients with bilaterally synchronous bursts, the percentages of time that paroxysmal formations were occurring were 4.9 during the control period with eyes closed, 2.7 during the control period with eyes open, and 2.0 during the psychological testing. One patient could not be included in this computation because all subtests were not given. For the 12 patients with focal bursts, the percentages during the control periods with eyes closed and with eyes open were 13.4 and 12.0, respectively. Suppression of burst activity during active thinking appeared to be the rule in

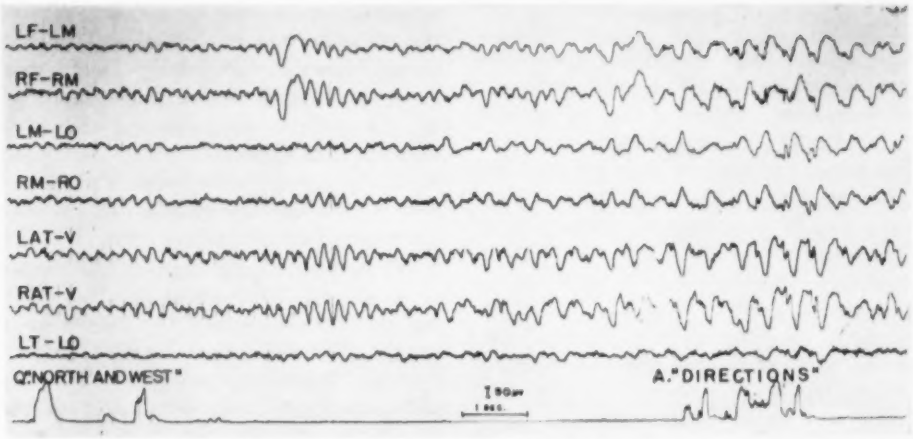


Fig. 4 (Patient 15).—Burst activity beginning prior to adequate answer and continuing throughout response period.

those patients with generalized bursts. This varied greatly, however, in patients with focal discharges. In one patient (No. 3), who at postmortem examination was found to have a glioma that extended from the left temporal lobe into the midbrain, the focal bursts, which lasted two to three minutes each, recurred episodically, apparently influenced little by the mental activity. In another patient (No. 20), whose bursts appeared most prominently over the frontal regions, a marked inhibition occurred during testing.

NR's and bursts were tabulated for subtest items according to their order of presentation (Fig. 5). It may be noted that there was a relatively small amount of burst activity during the beginnings of the subtests, with an irregular but progressive rise as testing proceeded. None of the points reached the control elevation of 11.2%. It may be observed that the occurrence of NR's roughly paralleled that of burst percentages. Percentages were based on from 101 to 105 observations for Points 1 through 10 and on 83 observations for Point 11. There were too few observations for each item beyond 11 for reliable comparison because administration of most subtests ended in this region.

An attempt was made to ascertain whether bursts were more highly associated with some parts of the question-response periods than with other parts. The trend was toward a higher proportion of burst time during questions and between question and response than during response. Suppression was least between end of response and next question. The figures were, respectively, 4.7%, 4.6%, 3.6%, and 6.7%. However, the trend was not consistent among subjects. For instance, percentage of burst time was consistently highest during responses for all subtests for one subject (No. 15).

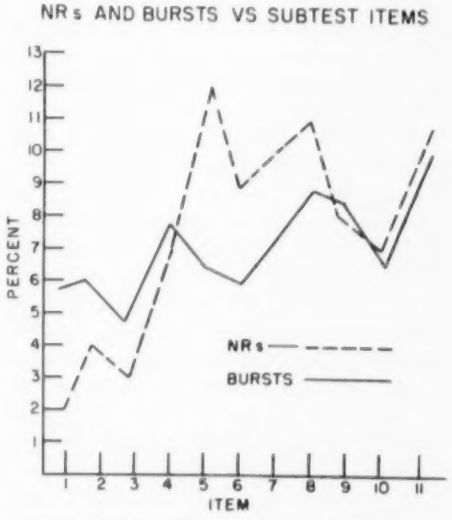


Fig. 5.—NR's and bursts versus subtest items.

Comment

It appears from the foregoing data that paroxysmal activity which would ordinarily be considered subclinical may in actuality be associated with demonstrable mental disturbances if appropriate tests are employed. These responses show up during psychological testing as inappropriate responses to test items, and may even include "don't-know" responses. Although it is common for examinees in general to give "don't-know" responses to items beyond their intellectual levels, some of the subjects in the current series did so to items well within their intellectual status when concurrent bursts were occurring. The identification of nonanswer responses as being related to intermittent larval bursts depends upon simultaneous psychological and electroencephalographic testing.

The disturbances of mental function observed in the present investigation cannot be directly compared with those described in previous studies,[1,4,8] since this earlier work described alterations of mental processes during actual petit mal attacks. However, it is useful to note the similarities and differences between the two sets of observations. Gastaut has pointed out that states of awareness vary greatly during petit mal seizures, and that a frequent finding is the preservation of perceptive functions and automatic activity, while cognitive functions and voluntary activity are diminished.[1] Jung has also noted that it is common for motor blocking to be present, although perception and memory for the stimulus are preserved.[4] Our findings appear to be consistent with these generalizations. We were repeatedly impressed by the retention of ability to perceive the question even when several seconds of burst activity occurred during the time the question was being asked. In rare instances it appeared that the question was heard but not understood, as indicated by a request for repetition of the question. Motor blocking could not be definitely established. Lengthening of response time could result from either motor blocking or disturbance of mental processes. In many instances it was clear that the ability both to verbalize and to retain the question were intact, the primary defect apparently being in the problem-solving area. We did not at any time observe an adequate solution to a problem during continuous bilaterally synchronous burst activity, although such was occasionally found during continuous focal discharges.

We have previously suggested that many of these responses might be considered "intellectual automatisms."[2] This concept implies that when burst activity is present there is a limitation of integrative processes and, consequently, an "acceptance" of the most immediate association to the test item.

Thought disturbances were seen in patients with both focal and generalized bursts. The success of psychological tests in revealing momentary alterations in thinking is probably in part related to the complexity of the integrative activity required for the solutions. Also, the tasks involved are relatively novel and cannot be dealt with entirely through learned reactivity. Thus, even when the paroxysmal abnormality is relatively discrete, there may be interference with a portion of the many integrative circuits involved.

Bursts were consistently suppressed during active thinking in patients with bilaterally synchronous bursts. This was also true for some of the patients with focal discharges. Suppression of burst activity was not unexpected, inasmuch as the effect of attention in blocking petit mal discharges has been noted repeatedly.[3,5] The psychological test situation might be one of the most effective for the inhibition of bursts, since almost continued attention to the task is a prerequisite for adequate performance. Li, Jasper, and Henderson stated that in some of their cases with petit mal the presentation of an arithmetic problem was the most effective arousal stimulus.[6] These same authors also reported that lesions involving diencephalic structures give rise to epileptiform activity which is susceptible to arousal stimuli but that focal cortical dis-

charges may not be influenced by similar stimuli. Beyond the general effect of the test procedure in reducing the incidence of bursts, there appeared to be a particular suppression during the first portion of each subtest. If degree of attention is the important variable, one might easily surmise that the initial portion of the subtest would represent the period of most critical interest. Later, the novelty of the test wanes, and bursts appear with increasing frequency.

Quadfasel and Pruyser have noted language difficulties in patients with psychomotor seizures and anterior temporal spikes.[7] An incidental finding in the current study was that 10 of the subjects occasionally showed verbal confusion, such as misusing common words or talking incoherently before ultimately giving an answer. Such expressions of confusion were associated with bursts almost half the time.

Summary

Twenty-one patients selected on the basis of having previously shown paroxysmal activity in EEG recordings were given portions of formal intelligence tests concomitantly with new EEG recordings. Electronic voice records were also made on the EEG tape to indicate when questions and answers were occurring.

Disturbances in higher integrative mental processes turned out to be significantly associated with paroxysmal cerebral activity. These disturbances were usually manifested during psychological testing by nonanswer responses (NR's), and, to a less extent, by "don't-know" responses and requests for repetition of the question, and occurred in the absence of overt seizures. NR's indicated transient losses of goal idea by verbal expressions of confusion or irrelevant remarks. Sometimes NR's and, more frequently, "don't-know" responses occurred in the absence of EEG bursts. Also, adequate answers sometimes occurred along with bursts.

Length of response time to test item was significantly related to amount of burst activity going on after presentation of item. Test performance was usually within or above the normal range during burst-free periods. Comprehension and retention of questions usually occurred even when bursts happened to be going on.

Burst activity tended to be suppressed during testing, when compared with control periods of the EEG recordings, especially in those patients with bilaterally synchronous bursts. Suppression was greatest near the beginning of each subtest.

Some of the most unexpected findings were individual variations from group trends.

Veterans' Administration Hospital, Fort Douglas Station (13).

REFERENCES

1. Gastaut, H.: The Brain Stem and Cerebral Electrogenesis in Relation to Consciousness, in Brain Mechanisms and Consciousness, edited by J. F. Delafresnaye, Springfield, Ill., Charles C Thomas, Publisher, 1954, pp. 249-279.

2. Hovey, H. B., and Kooi, K. A.: Transient Disturbances of Thought Processes and Epilepsy, A.M.A. Arch. Neurol. & Psychiat. 74:287-291, 1955.

3. Jung, R.: Über vegetative Reaktionen und Hemmungswirkung von Sinnesreizen im kleinen epileptischen Anfall, Nervenarzt 12:169-185, 1939.

4. Jung, R.: Correlation of Bioelectrical and Autonomic Phenomena with Alterations of Consciousness and Arousal in Man, in Brain Mechanisms and Consciousness, edited by J. F. Delafresnaye, Springfield, Ill., Charles C Thomas, publisher, 1954, pp. 310-339.

5. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, Arch. Neurol. & Psychiat. 36:1236-1250, 1936.

6. Li, C. L.; Jasper, H., and Henderson, L.: Effect of Arousal Mechanisms on Various Forms of Abnormality in the Electroencephalogram, Electroencephalog. & Clin. Neurophysiol. 4:513-526, 1952.

7. Quadfasel, A. F., and Pruyser, P. W.: Cognitive Deficit in Patients with Psychomotor Epilepsy, Epilepsia 4:80-90, 1955.

8. Schwab, R. S.: Influence of Visual and Auditory Stimuli on the Electroencephalographic Tracing of Petit mal, Am. J. Psychiat. 97:1301-1312, 1941.

9. Wechsler, D.: The Wechsler-Bellevue Intelligence Scale, Form II, New York, Psychological Corp., 1946.

10. Wechsler, D.: Wechsler Adult Intelligence Scale, New York, Psychological Corp., 1955.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Treatment, Neurosurgery

CENTRAL NERVOUS SYSTEM AND CARDIOVASCULAR EFFECTS OF RAUWOLFIA SERPENTINA. B. I. LEWIS, R. I. LUBIN, L. E. JANUARY, and J. B. WILD, J. A. M. A. 160:622 (Feb. 25) 1956.

Alseroxylon (derived from Rauwolfia serpentina) was administered in alternate courses with an identical placebo tablet to three groups of patients. Of these patients, 50 had had symptoms predominantly vascular, 50 were classified as having psychosomatic syndromes, and 10 were included as normal subjects for comparison. A daily dose of 4 mg. was arrived at as having satisfactory therapeutic effects with a minimum of undesired side-effects.

The results in the vascular patients proved difficult to interpret. In 20 hypertensive subjects the individual improvement was not related to the reductions in blood pressure and heart rate. The nature of the underlying mechanism of the improvement is unclear but all but 1 of a group of 15 patients with angina pectoris appeared to benefit from alseroxylon therapy.

All subjects with psychosomatic syndromes characterized by tension states improved. Sixteen subjects were followed for an average period of seven months each during alternate courses of alseroxylon and placebo. Fifteen improved with therapy. Seven relapsed on placebo, but the other eight maintained their gain during placebo administration. This was interpreted as an instance of the therapeutic prolongation pattern encountered in other phases of the investigation.

None of the patients with depressions, hysteria, or hypochondriasis was helped. In this series alseroxylon was most effective in managing the psychophysiological manifestations of tension states.

ALPERS, Philadelphia.

PHELANTIN FOR THE TREATMENT OF EPILEPSY. D. T. DAVIDSON and B. A. BERMAN, J. A. M. A. 160:766 (March 3) 1956.

Phelantin, a capsule combining 100 mg. of diphenylhydantoin sodium, 30 mg. of phenobarbital sodium, and 2.5 mg. of methamphetamine (Desoxyephedrine) hydrochloride, was given to 95 epileptic patients. Forty-eight, or approximately one-half of these, enjoyed complete freedom from seizures, and another eight had more than 50% improvement. Thirty-nine were less than 50% improved. In 80% of the completely controlled cases, the patients took Phelantin alone. The drug was more effective against grand mal convulsions than minor seizures. It is usually well tolerated, and no serious side-effects have been observed. Psychologically, patients benefit by the reduction in the number of pills prescribed. The essential ingredients of this capsule are less expensive in the form of Phelantin than when prescribed separately.

ALPERS, Philadelphia.

FIVE-YEAR STUDY OF BENZTROPINE (COGENTIN) METHANESULFONATE. L. J. DOSHAY, J. A. M. A. 162:1031 (Nov. 10) 1956.

Doshay considers benztropine (Cogentin) methanesulfonate, a synthetic agent that combines the active radicals of atropine and diphenhydramine (Benadryl) hydrochloride, an extremely valuable addition to the treatment of paralysis agitans. Benztropine is long-acting and hence needs to be used but once a day, at bedtime. It is employed to best advantage in combination with other anti-Parkinsonism agents, especially cerebral stimulants, which should be taken during the day. It has few side-effects, chief among them being slight dryness of the mouth, which disappears after breakfast.

This report records results obtained when benztropine was administered by mouth to 302 patients with various forms of Parkinsonism. The drug was found to have peripheral curariform effects that are long-lasting, cumulative, and very useful. Doses of 5 to 10 mg. thrice daily caused excessive flaccidity, to the extent that a patient was unable to lift his

arm or raise his head from the pillow. Best results, in the control of rigidity, contracture, tremor, and insomnia, were obtained in the dosage range of 1 to 4 mg. a day for older patients and 2 to 8 mg. a day for younger ones.

Abnormalities of gait, which troubled 56 patients, were alleviated in 35 of these. Three case histories are given to illustrate the relief from insomnia, night cramps, rigidity, and tremor: the recurrence of symptoms when the drug was temporarily withdrawn; the safety of continued use for more than five years, and the possibility of obviating side-effects, when they do occur, by simultaneous administration of phenindamine (Thephorin) and trihexyphenidyl.

Benztropine was found to exert a highly selective action against certain symptoms of Parkinsonism, such as no other current drug affords. Chief among these were the fixed facies, dysphonia, dysphagia, faulty posture, muscle cramps, and "freezing" of the legs.

ALPERS, Philadelphia.

PRIMARY CARE OF THE URINARY TRACT IN SPINAL CORD INJURY. H. S. TALBOT, J. A. M. A. 162:1203 (Nov. 24) 1956.

The structural changes that follow retention of urine in a paralyzed bladder must be prevented by adequate drainage from the beginning. With a catheter in place, the bladder regains its ability to fill and empty by reflex action with a certain regularity. It can be conditioned by the method of tidal drainage within a period of 6 to 12 weeks. Meanwhile a program of high fluid intake, acidulation of the urine, and muscular exercise is carried out to prevent lithiasis. The catheter can then be removed, and the observance of a certain program of fluid intake and other habits enable many patients to maintain an adequate urinary capacity, to empty the bladder completely, and to get along without wearing any apparatus.

Talbot points out that this method of treatment is not easy to follow. It requires meticulous daily attention to detail and seemingly endless explanations to all who are concerned in the patient's care. Above all, it demands the understanding and the willing cooperation of the patient, particularly during the difficult weeks of habit training after the removal of the catheter.

ALPERS, Philadelphia.

NEUROSURGICAL ASPECTS OF TREATMENT FOR PATIENTS WITH SPINAL CORD INJURIES. I. S. COOPER, J. A. M. A. 162:1205 (Nov. 24) 1956.

The first decision for the neurosurgeon after an injury to the spinal cord is whether any immediate neurosurgical maneuver is indicated. Neurological and roentgenographic examinations determine whether fracture-dislocation needs to be reduced, and whether post-traumatic fragments of bone, intraspinal hematomas, or herniated intervertebral disks require attention. In many cases early laminectomy is actually the conservative course of action.

Later problems for the neurosurgeon, from three months to several years after the injury, concern especially the intractable pain and spasticity that generally accompany paraplegia. Various procedures, including chordotomy, offer reasonable hope of relief of pain; alleviation of spasticity may be afforded by peripheral neurectomy, subarachnoid alcohol block, rhizotomy, or subtotal spinal chordectomy.

ALPERS, Philadelphia.

SURGICAL TREATMENT OF ARTERIOSCLEROTIC OCCLUSION OF THE COMMON CAROTID ARTERY. D. A. COOLEY, Y. A. NAAMAN, and C. A. CARTON, J. Neurosurg. 13:500 (Sept.) 1956.

The authors report a case of incomplete occlusion of the common carotid artery associated with arteriosclerotic changes within the vessel wall. No neurologic signs were present, and the patient's only complaint was that of a swishing noise in the head. An arteriogram revealed a partial occlusion of the common carotid artery just proximal to the bifurcation. At operation, thromendarterectomy was performed, and the artery was reconstructed, while a temporary external shunt was used to provide cerebral circulation. The authors state that prompt recognition and early treatment may prevent permanent neurologic deficit.

MANDEL, Philadelphia.

Muscular System

BENIGN CONGENITAL MYOPATHY WITH MYASTHENIC FEATURES. J. N. WALTON, N. GESCHWIND, AND J. A. SIMPSON, J. Neurol. Neurosurg. & Psychiat. 19:224 (Aug.) 1956.

The authors report the case of a woman who had developed muscular weakness and hypotonia at 9 months of age and then continued to show persistent but nonprogressive weakness, which was worse after exertion. Atrophy of the upper facial muscles, trunk, and limb muscles was present.

Metabolic and electrophysiological tests revealed no defect in carbohydrate or potassium metabolism. She was more resistant to decamethonium than the normal person and improved with ephedrine but not with edrophonium (Tensilon). Neostigmine (Prostigmin) produced a definite improvement in muscular power but resulted in increased weakness, particularly of the respiratory muscles, if the neostigmine was continued in moderate doses.

A muscle biopsy revealed only slight changes, which were compatible with a myopathic disorder.

The authors believe that this condition is best classified as a "congenital myopathy with myasthenic features." It was not possible to determine the nature of the biochemical or other defect in the muscle fiber or end-plate which was responsible for this patient's condition.

MANDEL, Philadelphia.

Encephalography, Ventriculography, and Roentgenography

PRIMARY EPIDERMOIDS OF THE SKULL. P. V. HAIG, Am. J. Roentgenol 76:1076 (Dec.) 1956.

Epidermoids of the skull are cystic areas in the bone the walls of which have three layers: (1) an outer layer, consisting of collagenic fibers with a few cells; (2) a middle layer, containing epithelial cells, and (3) an inner layer, consisting of parallel fibers. The content of the cyst has the appearance and consistency of putty and usually contains cholesterol crystals. Epidermoids have been found in all of the flat bones of the skull, all of the paranasal sinuses, and the maxilla, mandible, tympanum, and petrosa. The frontal bone and the temporal bone are the most frequent locations. The largest epidermoid which has been described in the medical literature is one about 9 cm. in diameter. Epidermoids are thought to arise as a result of anomalous embryonic development in which sequestration of epiderm occurs in the mesenchyme.

An epidermoid appears in roentgenograms as an area of bone destruction between the tables of the skull and shows a smooth margin of increased density. The larger ones will sometimes show a honeycombed appearance. Occasionally the epidermoid will penetrate the tables of the skull. An epidermoid occurring in the frontal sinuses is almost impossible to distinguish roentgenographically from a mucocele. Epidermoids can be cured by total excision of the entire cyst wall.

Haig reports the case of an old woman who developed a painful swelling at the bridge of her nose and the left side of her forehead. The roentgenograms were consistent with epidermoid. Biopsy was done, and the tumor was excised and found to be an epidermoid when examined histologically. The wound did not heal and gave off persistent drainage. A squamous-cell carcinoma developed in the wound about a year later. This is the third case which has been reported in the American medical literature in which an epidermoid has undergone malignant change.

WEILAND, Grove City, Pa.

Serum Copper and Oxidase Activity in Schizophrenic Patients

Correlations with Erythrocyte Sedimentation Rate, C-Reactive Protein, Ascorbic Acid, Basal Metabolic Rate, and Sulfobromophthalein (Bromsulphalein) Retention Tests

M. K. HORWITT, Ph.D.; B. J. MEYER, M.B., Ph.D.; A. C. MEYER, Ph.D.; C. C. HARVEY, Ph.D., and D. HAFFRON, M.D., Elgin, Ill.

The possibility that the metabolism of epinephrine and of other amines may be altered in schizophrenia, the observation that plasma copper is increased during chlorpromazine therapy,[1] and the knowledge that ceruloplasmin, a copper-protein in serum which varies with stress situations, can oxidize epinephrine have stimulated research on copper in serum of mental patients. A recent claim by Akerfeldt[2] that the fresh blood serum from mental patients had the capacity to oxidize N, N-dimethyl-*p*-phenylenediamine more rapidly than fresh serum from healthy control subjects, and that this increased oxidizing activity of serum from mental cases was probably due to an increase in ceruloplasmin in the serum of mental patients makes it pertinent to review the factors which affect this and related reactions.

Except for a marked decrease in ceruloplasmin in serum of patients with hepatolenticular degeneration and in some patients with the nephrotic syndrome, the blood levels of this protein usually increase in long-term stress situations. Markowitz et al.[3] have reviewed these changes with special reference to the effects of pregnancy, infections, and neurological disorders. In most groups studied, the copper concentration of the serum could be directly correlated with the ceruloplasmin content, so that, in effect, a careful copper determination might be substituted for either the direct determination of ceruloplasmin or its phenylenediamine oxidase activity.

Claims that blood copper levels are increased during schizophrenia have been made[4] and denied.[5] As average serum copper levels for women are somewhat higher than those for men, attempts have been made to determine the effects of menstruation,[6,7] but no definite correlations between serum copper levels and the time of the menstrual cycle have, as yet, been proved. Small diurnal variations in plasma[7] and serum copper[6] have been observed and need reinvestigation in view of the possible importance of the time of sample withdrawal. Leach et al.[8] have studied the role of ceruloplasmin on the oxidation of epinephrine and have confirmed the report by Holmberg and Laurell[9] that ceruloplasmin can oxidize epinephrine in vitro. It appears unlikely

Submitted for publication May 17, 1957.

From the Biochemical Research Laboratory, Elgin State Hospital.

Supported by grant-in-aid from the Illinois Mental Health Fund and the National Institutes of Health (A-1126).

that this reaction can take place in vivo in the presence of traces of ascorbic acid and of other reducing substances which are present in normal blood; nevertheless, it may prove significant when we know more about the mechanisms involved.

The six-minute oxidation of N, N-dimethyl-*p*-phenylenediamine by serum, a test reported by Akerfeldt,[2] appears to have limited value when applied without nutritional controls, as any ascorbic acid in the serum may not be fully oxidized during this short test period and may inhibit the reaction. Recommended instead is the 60-minute incubation technique described by Ravin,[10] who makes use of *p*-phenylenediamine hydrochloride as a substrate to estimate ceruloplasmin. The latter test employs better controls of pH and of the possible presence of oxidase inhibitors, and uses smaller concentrations of serum during longer incubation periods, minimizing the effects of active reducing substances in the serum. Another test, designed by Abood,[11] makes use of *p*-phenylenediamine solutions at a somewhat higher pH and gives essentially similar results.

It is improbable that anything as nonspecific as an increase in serum ceruloplasmin will prove useful in the identification of a particular disease. Changes in this copper-protein may be associated with a nonspecific shift in the globulins.[12] More important is the need for better understanding of the biochemistry of this stress phenomenon: What causes these changes, and are they harmful or useful to the organism?

Methods

The experiments reported here make use of some subjects who have been observed in a metabolic study[13] for over three years, during which time their dietary intake and environment have been exactly controlled. In addition, schizophrenic patients who had been either newly admitted or just readmitted to this hospital were also studied. Nursing students, staff, and laboratory personnel were used as "normals." Except where otherwise indicated, blood samples were drawn before breakfast.

Three different techniques were used, simultaneously, on aliquots of the same blood sample, to estimate the oxidative activity of ceruloplasmin in the serum of most of the subjects studied.

(*a*) The Akerfeldt[2] test measures the increase in density at 552mμ produced in six minutes when one part of serum is mixed with one part of 0.1% N,N'-dimethyl-*p*-phenylenediamine dihydrochloride solution. Temperature control was found to be necessary and was facilitated by circulating water at 25 C around the cuvette well of the Beckman DK2 Ratio Recording Spectrophotometer employed. A "time drive" was installed in this instrument in order to simplify the visualization of changes in the rate of the reaction with time.

(*b*) The test described by Ravin[10] combines 0.1 ml. of serum with 1 ml. of 0.5% *p*-phenylenediamine hydrochloride and 2 ml. of 0.1 N acetate buffer, pH 6.0, at 37 C for 60 minutes, after which the reaction is inhibited by adding 1 ml. of 0.1% sodium azide. After diluting with 6 ml. of 3% sodium chloride solution, the increase in color is measured against a sodium-azide-inhibited control at 525mμ in a Beckman Model B.

(*c*) Abood's test[11] mixes 0.1 ml. of serum with 0.1 ml. of 0.1% *p*-phenylenediamine and 1 ml. of 0.05 M tris (hydroxymethyl) aminoethane buffer at pH 7.0. After 60 minutes at 37 C, 1.8 ml. of water is added and the color produced read against water at 490mμ. The data recorded for all the above reactions are relative color densities (increase in absorbance) obtained by using a 10 mm. optical path.

Copper in serum was determined by the method of Gubler et al.[14]; ascorbic acid, by the technique of Mindlin and Butler.[15] Erythrocyte sedimentation rate, hemoglobin, hematocrit (Wintrobe), and sulfobromophthalein (Bromsulphalein) retention (5 mg. per kilogram for 45 minutes) were determined by standard techniques.[16] Basal metabolic rates were estimated by means of a Sanborn metabulator. The C-reactive protein test was conducted by using a capillary precipitin reaction with a specific rabbit antihuman C-reactive protein antiserum.*

Results

Correlation of Serum Copper with Oxidase Activities.—Table 1 presents, in the order of their serum copper concentration, the serum oxidase activities of 36 newly admitted or readmitted male patients in acute relapse, diagnosed as schizophrenic. Table 2 presents the data from 30 female patients with schizophrenia. Where data for

* Provided by Schieffelin & Company, New York.

TABLE 1.—*Data on Newly Admitted or Readmitted Male Schizophrenic Patients (Random Selection)*

Patient No.	Age, Yr.	Duration of Illness,* Time	No. of Previous Admissions	Serum Copper, γ/100 Ml.	Relative Oxidase Activity (Absorbance per 10 Mm.) Ravin At 525mμ	Abood At 490mμ	Akerfeldt At 552mμ	Serum Ascorbic Acid, Mg/100 Ml.	Erythrocyte Sedimentation Rate, Mm/Hr.
1	35	10 yr.	2	98	0.40	0.18	0.48		19
2†	31	4 days	0	99	0.41	0.16	0.20	0.96	
3†	14	18 days	0	101	0.32	0.16	0.32		12
4†	32	4 yr.	1	102	0.40	0.16	0.52	0.43	
5	35	10 yr.	1	102	0.24	0.13	0.44	0.41	
6	34	12 yr.	2	108	0.41	0.14	0.37		
7†	27	11 days	0	110	0.48	0.42	0.59		
8†	21	18 days	0	111	0.36	0.17	0.18		
9†	26	3 yr.	?	111	0.43	0.19	0.35		
10	29	3 yr.	4	112	0.39	0.16	0.39		
11	25	4 yr.	5	116	0.45	..	0.35		
12†	31	4 yr.	1	118	0.45	0.18	0.48		
13†	37	30 days	0	120	0.38	0.23	0.32	0.68	
14†	16	25 days	0	120	0.38	0.16	0.28		
15	29	7 yr.	2	120	0.35	0.14	0.08		
16	31	4 yr.	5	120	0.32	0.16	0.38		
17†	49	31 days	0	120	0.48	0.20	0.45		
18	29	?	1	123	0.45	0.18	0.45		
19†	35	17 yr.	7	124	0.48	0.26	0.62		
20†	23	4 yr.	1	124	0.36	0.24	0.48	0.49	
21	27	10 yr.	4	126	0.39	0.20	0.54	0.41	
22	20	2 yr.	2	126	0.44	0.20	0.60	0.34	
23	36	10 yr.	1	129	0.45	0.20	0.65		
24	46	1 yr.	1	132	0.53	0.18	0.40		
25†	33	2 mo.	0	133	0.49	0.17	0.40		
26†	31	9 days	2	134	0.48	0.18	0.58		
27	33	3 yr.	1	137	0.47	0.18	0.42		
28	32	16 yr.	5	140	0.50	0.22	0.63	0.49	
29†	32	10 days	0	142	0.61	0.28	0.67	0.45	
30	31	3 yr.	4	142	0.39	0.22	0.55	0.41	28
31†	38	29 days	0	142	0.54	0.21	0.34		41
32†	30	16 days	0	146	0.45	0.26	0.74		
33†	37	2 mo.	0	150	0.61	0.27	0.59		24
34	33	3 yr.	1	150	0.45	0.21	0.62		
35†	24	10 days	0	156	0.38	0.23	0.49	0.56	
36	43	3 yr.	1	222	0.82	0.50	0.85		51
Average				126.8±22.5	0.443±0.100	0.209±0.074	0.467±0.161		

* Duration of illness based upon date of first hospital admission.
† Patients who had no record of any organic treatment.

TABLE 2.—*Data on Newly Admitted or Readmitted Female Schizophrenic Patients (Random Selection)*

Patient No.	Age, Yr.	Duration of Illness,* Time	No. of Previous Admissions	Serum Copper, γ/100 Ml.	Relative Oxidase Activity (Absorbance per 10 Mm.) Ravin At 525mμ	Abood At 490mμ	Akerfeldt At 552mμ	Serum Ascorbic Acid, Mg/100 Ml.	Erythrocyte Sedimentation Rate, Mm/Hr.
1	18	1 yr.	1	89	0.34	0.13	0.25		
2†	37	2 mo.	0	89	0.27	0.12	0.48	0.48	18
3†	23	3 days	0	98	0.38	0.19	0.37		28
4	24	7 yr.	5	104	0.40	0.17	0.17	1.41	
5	38	8 yr.	1	105	0.46	0.18	0.48		
6	30	4 yr.	6	108	0.36	0.15	0.60	0.48	
7	39	9 yr.	6	117	0.33	0.17	0.56	0.31	
8†	35	10 days	0	118	0.46	0.18	0.62	0.26	
9	29	6 yr.	4	118	0.43	0.19	0.49	0.29	
10	48	2 yr.	1	120	0.28	0.15	0.28	1.07	
11	44	2 yr.	1	120	0.39	0.17	0.43	0.38	
12	33	4 days	0	122	0.38	0.17	0.43	1.37	
13	40	8 yr.	8	123	0.37	0.22	0.34	1.39	
14†	20	12 days	0	124	0.50	0.28	0.73		
15	46	10 yr.	3	125	0.44	0.18	0.77	0.37	34
16	31	1 yr.	1	131	0.35	0.18	0.51	0.66	
17	27	2 yr.	5	132	0.45	0.21	0.57	0.54	
18	23	4 yr.	1	135	0.38	0.18	0.35	0.75	
19	40	15 yr.	7	138	0.56	0.34	0.74	0.70	
20	65	28 yr.	2	139	0.51	0.26	0.66	0.77	
21	42	17 yr.	5	144	0.54	0.20	0.54	0.76	11
22	29	9 yr.	1	147	0.32	0.19	0.34		44
23	30	10 yr.	6	149	0.47	0.25	0.58		
24†	31	3 days	0	152	0.65	0.21	0.68		
25	40	8 yr.	7	154	0.52	0.23	0.56	0.26	40
26	29	8 yr.	1	157	0.50	0.21	0.47	0.98	
27	42	2 yr.	2	157	0.57	0.29	0.66	0.77	28
28	56	20 yr.	8	164	0.60	0.26	0.74	1.58	
29	32	9 yr.	4	173	0.57	0.24	0.52	1.22	
30‡	32	4 yr.	2	(208)	(0.92)	(0.51)	(1.20)	0.77	47
Average				129±22.0	0.441±0.099	0.205±0.050	0.514±0.153		

* Duration of illness based upon date of first hospital admission.
† Patients who had no record of any organic treatment.
‡ Patient four months' pregnant; not included in average.

TABLE 3.—*Normal Controls (Male)*

Subject No.	Age, Yr.	Serum Copper, γ/100 Ml.	Relative Oxidase Activity (Absorbance per 10 Mm.) Ravin At 525mμ	Abood At 490mμ	Akerfeldt At 552 mμ	Ascorbic Acid, Mg/100 Ml.
1	29	93	0.29	0.19	0.02	1.00
2	19	98	0.40	0.17	0.00	1.26
3	60	101	0.36	0.19	0.28	1.06
4	51	109	0.44	0.18	0.21	1.36
5	28	114	0.54	0.20	0.46	0.70
6	24	114	0.36	0.16	0.21	1.00
7	45	114	0.49	0.17	0.31	1.26
8	49	119	0.47	0.21	0.49	0.70
9	19	124	0.38	0.19	0.23	1.24
10	37	137	0.47	0.27	0.56	1.10
Average		112.3±13.0	0.420±0.075	0.193±0.031	0.286±0.170	

ascorbic acid level and sedimentation rate (analyzed simultaneously) were available, they are included in these Tables. Tables 3 and 4 tabulate similar data from analyses of serum from members of the staff, laboratory assistants, and student nurses.

There is little to distinguish the data for patients with schizophrenia from those for normal subjects, although most of the mental subjects summarized in Tables 1 and 2 were known to be schizophrenic patients in an acute stage of the disease. Blood from these patients was drawn prior to the institution of any organic treatment. It is reasonable to anticipate that severe emotional stress, like other stresses, may produce higher levels of ceruloplasmin, although no such correlation could be noted among the more disturbed subjects examined in this study. As with the normal subjects, the low and high serum copper levels are associated with the corresponding extremes of oxidase activity, but in the large middle group there is considerable overlapping.

Constancy of Basal Levels of Serum Copper.—To evaluate possible variations of serum ceruloplasmin with time, a mixed group of subjects were reexamined after a 25- to 28-day interval for their serum copper and oxidative activities by the Ravin method. Where enough serum was available, the Abood and Akerfeldt tests were also performed. Table 5 demonstrates that, with few exceptions, the serum copper and oxidase activities of the subjects studied were quite constant. Data from samples taken at the beginning of this experiment listed under (*a*) are arranged in order of increasing serum copper concentrations. It is to be noted that changes in copper level, when they do occur, are usually reflected in similar changes in the results of the Ravin test.

TABLE 4.—*Normal Controls (Female)*

Subject No.	Age, Yr.	Serum Copper, γ/100 Ml.	Relative Oxidase Activity (Absorbance per 10 Mm.) Ravin At 552mμ	Abood At 490mμ	Akerfeldt At 552mμ	Ascorbic Acid, Mg/100 Ml.	Erythrocyte Sedimentation Rate, Mm/Hr.
1	22	78	0.20	0.18	0.04	1.4	4
2	20	82	0.35	0.12	0.25	1.02	5
3	20	98	0.34	0.14	0.04	1.20	14
4	20	106	0.37	0.18	0.26	0.68	24
5	20	106	0.39	0.22	0.50	0.58	21
6	20	106	0.42	0.18	0.30	0.90	20
7	20	120	0.41	0.18	0.39	0.96	15
8	20	122	0.42	0.21	0.54	0.57	11
9	21	130	0.47	0.16	0.33	0.64	31
10	19	130	0.40	0.20	0.59	0.60	22
11	57	132	0.47	0.23	0.55	1.03	
12	55	136	0.49	0.21	0.56	0.50	
13	55	143	0.49	0.25	0.46	1.16	
14	21	160	0.56	0.24	0.63	1.08	22
Average		117.8±23.1	0.420±0.070	0.191±0.035	0.389±0.193		

TABLE 5.—*Constancy of Basal Levels of Serum Copper and Oxidase* *
(Blood Samples for Series (*a*) and (*b*) Taken Approximately 27 Days Apart)

Subject No.†	Serum Copper, γ/100 Ml.		Relative Oxidase Activity (Absorbance per 10 Mm.) Ravin O. D. at 525mμ		Abood O. D. at 490mμ		Akerfeldt O. D. at 552mμ	
	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)	(*a*)	(*b*)
1 NF	78	78	0.30	0.25	0.18	0.16	0.04	0.02
2 SF	89	105	0.27	0.37	..	..	..	..
3 SF	98	101	0.32	0.32	..	..	..	..
4 SF	98	122	0.38	0.40	..	..	..	..
5 SM	98	126	0.40	0.52	..	..	..	..
6 NF	98	105	0.34	0.34	0.14	0.19	0.04	0.06
7 NF	106	95	0.37	0.34	0.18	0.18	0.26	0.05
8 NF	106	111	0.39	0.38	0.22	0.19	0.50	0.52
9 NF	106	114	0.42	0.43	0.18	0.20	0.30	0.35
10 NF	120	116	0.41	0.35	0.18	0.17	0.39	0.24
11 NF	122	121	0.42	0.42	0.21	0.20	0.54	0.53
12 NF	130	134	0.47	0.44	0.16	0.22	0.33	0.28
13 NF	130	144	0.40	0.59	0.20	0.31	0.59	0.81
14 SF	144	154	0.54	0.54	..	..	..	..
15 SM	150	142	0.56	0.54	..	..	..	..
16 SF	154	122	0.52	0.32	..	..	..	..
17 SF	157	144	0.50	0.42	..	..	..	..
18 NF	160	154	0.56	0.49	0.24	0.28	0.63	0.45
19 SM	167	150	0.62	0.61	..	..	..	..
20 SM	188	142	0.69	0.61	..	..	..	..
21 SM	208	222	0.83	0.82	..	..	..	..
22 SF	268	270	0.92	0.94	..	..	..	..

* Subjects selected to include more high and low initial copper levels.
† F=female subjects; M, male subjects; N, normal subjects; S, schizophrenic patients.

Diurnal Variations.—As the above data were obtained on blood drawn before breakfast, it appeared necessary to evaluate whether samples taken at later periods have different copper and oxidase levels, since most other investigators working in this field take blood after breakfast. Table 6 presents the results obtained in such a study. Breakfast was eaten at 7 a.m. and lunch at 12 p.m. Data on hematocrit levels are included to assist in the evaluation of the erythrocyte sedimentation rate. A similar study on four other patients, which included samples taken until 11 p.m., gave no additional information and is not presented here. The minor fluctuations in copper levels noted in Table 6 are not significant, indicating that the time of blood-sample withdrawal is not crucial in this particular study. The minor fluctuations in the erythrocyte sedimentation rate were not significant in this series.

Comparison of Basal Serum Copper Levels and Oxidase Activity with Basal Metabolic Rate, Sedimentation Rate, C-Reactive Protein Test, and Sulfobromophthalein Retention.—A group of male schizophrenics, whose nutritional intake,

TABLE 6.—*Diurnal Variation in Serum Copper and Oxidase Activity*

Patient No.	Time	Serum Copper, γ/100 Ml.	Ravin O. D. per 10 Mm. At 525mμ	Hematocrit	Erythrocyte Sedimentation Rate, Mm/Hr.
1	6:45	150	0.45	44.8	35
	9:45	145	0.44	42.6	22
	11:45	146	0.48	42.1	23
	2:45	143	0.41	41.4	24
2	6:45	138	0.38	44.0	20
	9:45	138	0.36	43.4	21
	11:45	142	0.42	43.1	20
	2:45	140	0.37	45.4	25
3	6:45	110	0.31	40.0	9
	9:45	110	0.30	40.0	9
	11:45	114	0.33	40.0	10
	2:45	114	0.34	39.5	11
4	6:45	141	0.43	53.0	15
	9:45	143	0.41	53.0	14
	11:45	150	0.46	53.0	14
	2:45	143	0.39	52.5	16

TABLE 7.—*Serum Copper Level and Oxidase Activity Related to Basal Metabolic Rate, Liver Function, and Possible Inflammatory Processes (Controlled Environment*)*

Patient No.	Serum Copper, γ/100 Ml.	Ravin O. D. per 10 Mm. At 525mμ	BMR	Sulfobromophthalein Retention, %	Hematocrit	Erythrocyte Sedimentation Rate, Mm/Hr.	C-Reactive Protein
1	84	0.31	−7	4.3	44.0	13	−
2	96	0.34	−14	2.9	40.0	9	−
3	98	0.37	−5	2.6	46.5	3	−
4	100	0.35	−16	4.9	48.0	4	−
5	105	0.37	−15	5.0	42.0	12	−
6	110	0.37	−13	4.5	53.0	15	−
7	112	0.42	−19	5.1	44.0	18	−
8	112	0.38	−2	2.0	50.0	12	−
9	112	0.39	0	5.1	47.0	3	−
10	114	0.36	−18	1.1	47.0	6	−
11	114	0.37	−17	2.6	46.5	7	−
12	118	0.35	−23	10.0	40.0	17	−
13	118	0.39	−12	1.0	42.5	33	−
14	120	0.36	−3	5.7	46.0	22	+
15	120	0.36	+2	2.1	41.0	11	−
16	122	0.38	−6	5.7	44.0	20	−
17	122	0.33	−10	2.6	42.5	10	−
18	122	0.40	−15	4.2	44.8	21	+
19	122	0.45	−9	5.7	45.0	9	−
20	122	0.43	+2	3.1	42.0	15	−
21	123	0.46	−9	4.0	48.0	11	−
22	125	0.39	+10	7.9	48.0	17	−
23	128	0.38	−6	0.7	44.0	10	−
24	128	0.36	−2	1.8	50.0	9	−
25	132	0.36	−19	7.0	46.5	7	−
26	136	0.39	+6	1.0	41.0	17	−
27	136	0.44	−14	2.2	45.0	20	−
28	142	0.45	−11	8.3	44.0	29	+
29	150	0.47	−5	3.8	44.8	25	+
30	154	0.44	−17	11.9	41.0	11	−
31	154	0.44	−19	3.8	46.0	28	+
32	154	0.44	+1	0.6	48.8	18	+
33	154	0.51	−3	2.6	42.3	5	−
Average	122.9±24.9	0.394±0.046					

*All patients in this Table are male and have been under special observation, including careful dietary control, for over three years

environment, and physiological state had been meticulously controlled for over three years, were examined in the hope that variations in the serum copper of such subjects might be more readily interpreted (Table 7). Most of these subjects have been in this institution for many years. The hematocrit values of these patients are included for better evaluation of their relatively high sedimentation rates. In an attempt to explain at least some of these high sedimentation rates, the C-reactive protein test [17] was performed simultaneously. The latter test indicates that in some cases inflammatory processes or other organic lesions might be responsible for the high

TABLE 8.—*Relationship of Serum Copper Level, Oxidase Activity, Erythrocyte Sedimentation Rate, and C-Reactive Protein Activity in Normal and Schizophrenic Male Subjects*

Subject No.*	Age, Yr.	Serum Copper, γ/100 Ml.	Ravin O. D. per 10 Mm. At 525mμ	Sedimentation Rate, Mm/Hr.	C-Reactive Protein
1 S	14	98	0.29	9	−
2 S	40	105	0.35	2	−
3 S	43	105	0.34	6	−
4 N	25	112	0.37	9	−
5 S	31	118	0.37	8	−
6 N	24	122	0.41	5	−
7 N	55	130	0.38	13	−
8 S	55	132	0.39	10	−
9 S	30	132	0.39	23	−
10 N	30	135	0.41	15	−
11 N	28	137	0.40	8	−
12 N	19	137	0.39	7	−
13 N	21	142	0.45	20	−
14 N	22	146	0.44	7	+
15 S	55	159	0.53	22	+
16 N	24	166	0.51	33	−
17 N	55	166	0.52	41	+
18 S	33	174	0.63	17	+

*S = schizophrenic patients, newly admitted; N, newly arrived employees.

sedimentation rate and high serum copper level. Four of the six positive C-reactive protein reactions (Table 7) are associated with increased sedimentation rates and elevated serum copper levels (also note sedimentation rates in Tables 1, 2, and 4).

To evaluate further the higher serum copper levels and oxidase activities noted in some of the subjects studied, the copper level, oxidase activity (Ravin), sedimentation rate, and C-reactive protein activities were determined in a group of newly arrived male hospital employees, some of whom may be considered to represent a distressed group, economically, and compared with another group of newly admitted or readmitted mental patients. The results are listed according to serum copper levels in Table 8 and point to the importance of complete physical and laboratory examinations before any conclusions about serum coper and oxidase activity are justified.

So far as can be determined from evaluating the basal metabolic rates and the sulfobromophthalein retentions, the subjects under study had no obvious abnormalities of thyroid[18] or liver function that could be correlated with serum copper levels.

Comment

The data presented offer little or no support for the suggestion that phenylenediamine oxidase activities of the serum of schizophrenic patients are higher than those found in "normals." The six-minute test used by Akerfeldt will be positive in many institutionalized schizophrenics, but this is often a function of the low ascorbic acid level of the diet of many institutions.[19] However, it should be noted that when the serum copper is high, the effect of ascorbic acid in inhibiting the oxidation is minimized. Because most of the ascorbic acid inhibition of oxidase activity is completed within a few minutes, tests which make use of 60-minute incubation periods are less affected by ascorbic acid in the serum. The question as to whether copper and/or ascorbic acid levels of the blood are altered at all by emotional stresses, in a manner similar to the way they are affected by the stresses of infection or pregnancy, remains to be evaluated, but the experimental methods which will be required to estimate such changes will have to be more precise than any that have been utilized to date.

This incidence of minor infections, like gingivitis, fungous infections, etc., is apparently as high in the newly admitted employees hired to work at low salary rates as in newly admitted patients. Such minor chronic infections may be the cause of some of the higher copper levels noted.

From the data reported, one may conclude that serum copper levels or tests of oxidation of phenylenediamine, or its derivatives, are not, in their present form, definitive for evaluating mental illness. Not only is there the possibility that nonspecific stress may play a role in elevating serum copper-proteins, just as other plasma globulins are increased by stress reactions, but also the variable effects of nutritive states and of minor organic lesions must be evaluated before any simple test of the type suggested is given credence.

Summary

Total serum copper and the rate of oxidation by serum of phenylenediamine derivatives were determined in schizophrenic patients and in normal subjects. The data obtained do not show any important differences that could be used for diagnostic purposes.

As infections and inflammatory reactions are known to increase serum copper and ceruloplasmin concentrations, an attempt was made to correlate sedimentation rate and C-reactive protein with increases in serum copper-containing compounds. Such a relationship was confirmed in some of the subjects.

Short-term tests (six minutes) of the rate of ceruloplasmin phenylenediamine oxidase activity are difficult to interpret because variable amounts of reducing compounds, like ascorbic acid, strongly inhibit the oxi-

dations involved. Tests which make use of longer incubation periods and smaller amounts of serum are proportionately less affected by the nutritional artifacts which, in part, control the concentration of ascorbic acid and other reducing agents in the blood.

Higher copper levels in the serum might be expected to increase the rate of oxidation of many compounds like epinephrine, ascorbic acid, phenylenediamines, and glutathione in vitro. Whether such oxidations are also accelerated by copper compounds in vivo remains to be determined. In any case, such high copper levels have not been satisfactorily related to the mental disorders studied.

There is no apparent justification for conducting serum phenylenediamine oxidation tests in the study of mental patients unless other tests of organic disability are conducted simultaneously.

Tests for evaluating the basal metabolic rate and sulfobromophthalein (Bromsulphalein) retention were performed in order to estimate how minor variations in basal metabolism and liver function might affect the levels of serum copper. No significant correlations could be made from such data.

Dr. G. D. Duncan and Dr. B. Century gave professional biochemical assistance; Mr. E. Harmon, Mr. V. Likhite, Mrs. Mary Turner, and Mrs. Edna Newtson, technical assistance; Dr. L. Abood, advice on the modification of the method he used, and Dr. Percival Bailey, support and encouragement.

Elgin State Hospital.

REFERENCES

1. Azima, H., and Richman, A.: Alteration of Copper Metabolism in Chlorpromazine-Treated Cases, A. M. A. Arch. Neurol. & Psychiat. 75:163, 1956.

2. Akerfeldt, S.: Oxidation of N,N'-Dimethyl-p-phenylenediamine by Serum from Patients with Mental Disease, Science 125:117, 1957.

3. Markowitz, H.; Gubler, C. J.; Mahoney, T. P.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: XIV. Copper, Ceruloplasmin and Oxidase Activity in Sera of Normal Human Subjects, Pregnant Women, and Patients with Infection, Hepatolenticular Degeneration and the Nephrotic Syndrome, J. Clin. Invest. 34:1498, 1955.

4. Heilmeyer, L.; Keiderling, W., and Stüwe, G.: Kupfer und Eisen als körpereigene Wirkstoffe und ihre Bedeutung beim Krankheitsgeschehen, Jena, Gustav Fischer, 1941.

5. Munch-Petersen, S.: On Serum Copper in Patients with Schizophrenia, Acta psychiat. et neurol. scandinav. 25:423, 1950.

6. Nielsen, A. L.: On Serum Copper: III. Normal Values, Acta med. scandinav. 118:87, 1944.

7. Lahey, M. E.; Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: VI. Blood Copper in Normal Human Subjects, J. Clin. Invest. 32:322, 1953.

8. Leach, B. E., and Heath, R. G.: The in Vitro Oxidation of Epinephrine in Plasma, A. M. A. Arch. Neurol. & Psychiat. 76:444, 1956.

9. Holmberg, C. G., and Laurell, C. B.: Investigations in Serum Copper: III. Ceruloplasmin as an Enzyme, Acta chem. Scandinav. 5:476, 1951.

10. Ravin, H. A.: Rapid Test for Hepatolenticular Degeneration, Lancet 1:726, 1956.

11. Abood, L.: Work Reported at Meeting of Brain Research Foundation, Chicago, Jan. 12, 1957; personal communication to the authors.

12. Cumings, J. N.; Goodwin, H. J., and Earl, C. J.: Blood Copper and Its Relationship to the Globulins, J. Clin. Path. 8:69, 1955.

13. Horwitt, M. K.; Harvey, C. C.; Duncan, G. D., and Wilson, W. C.: Effects of Limited Tocopherol Intake in Man with Relationships to Erythrocyte Hemolysis and Lipid Oxidations, Am. J. Clin. Nutrition 4:408, 1956.

14. Gubler, C. J.; Lahey, M. E.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: Method for Determination of Copper in Whole Blood, Red Cells and Plasma, J. Biol. Chem. 196:209, 1952.

15. Mindlin, R. L., and Butler, A. M.: Determination of Ascorbic Acid in Plasma: A Macromethod and Micromethod, J. Biol. Chem. 122: 673, 1938.

16. Hepler, O. E.: Manual of Clinical Laboratory Methods, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1953.

17. Roantree, R. J., and Rantz, L. A.: Clinical Experience with the C-Reactive Protein Test, A. M. A. Arch. Int. Med. 96:674, 1955.

18. Nielsen, A. L.: Serum Copper: V. Thyrotoxicosis and Myxoedema, Acta med. scandinav. 118:431, 1944.

19. Horwitt, M. K.: Studies in Human Nutrition: I. Ascorbic Acid Requirement of Individuals in a Large Institution, Proc. Exper. Biol. & Med. 49:248, 1942.

Need for a New Subdiscipline in the Medical Profession*

LAWRENCE S. KUBIE, M.D., New York

Almost unrecognized, a revolution in the personnel of our major social and political institutions is occurring. Under various names, a new Man is appearing on their tables of organization. The ivory-tower scholar of the past is participating in the practical affairs of life. Where he used to be ridiculed or disguised, he now is accepted on his own terms. This is a symptom of a maturing culture—that economists, sociologists, historians, legal scholars, psychologists, and anthropologists are emerging from their classrooms and laboratories to the board rooms of industry, finance, and government.

Perhaps even more revolutionary is the fact that the same thing is happening to the physician who is trained in psychodiagnosis and in psychotherapy. He is graduating from the hospital, the private consulting room, the classroom, and the laboratory to reexamine the ways in which we live and work and play, in which we organize family life and try to raise free and healthy children for the free and healthy adult world of which we dream. This development grows out of our deepening awareness of the fact that to be a human being is a task of infinite and subtle complexity, to which the well-known human race, with all of its cultural institutions, has not yet proved itself equal. This humble acceptance of limitations includes an acknowledgment that we have never met man's most important responsibility adequately, namely, to bring up children who will be healthier than ourselves. Parents who are graced by even a faint flush of decent humility are coming to recognize the fact that every child needs an adult ally outside his own small, immediate family. Today our family units and the houses in which we live are too small to supply this. When sprawling and abundant families lived together with their collaterals under one roof, each child had at least a chance to find such an ally. But this is a role that no one fills today—not the priest or the pediatrician or the teacher. Therefore, the psychiatrist is constantly called upon to try to supply what is needed. But there are too few of us, and of these only few are trained for it.

Meanwhile, simultaneously the obstetrician in the delivery room, the educators in nursery and kindergarten, in grade and high school, in colleges and graduate and professional stratospheres of education, all are seeking whatever light the psychiatrist can throw on their problems. Competing for his services are children's courts, domestic relations courts, criminal courts, reformatories and prisons, probation officers, and every other organized effort at rehabilitation. In industry his help is sought in personnel work, in the allocation of men to proper tasks, in grading loads to a man's capacity, in sheltered workshops. He is sought by every variety of social agency and by churches to deal with the human problems of parishioners. Sometimes his aid is sought even on larger issues of national and international import. At the same time, and to an ever-increasing extent, he is invited to share in the healing work of the medical

* Special article.

Submitted for publication March 6, 1957.

Read before the Strecker Society, Philadelphia, Dec. 10, 1956.

Clinical Professor of Psychiatry, Yale University School of Medicine; Faculty, New York Psychoanalytic Institute; Lecturer in Psychiatry, Columbia University College of Physicians and Surgeons.

and surgical wards of adult and pediatric services, of all the specialist services in general hospitals, and in every outpatient clinic, and especially in the institutions which are growing up to care for the long-lived sufferers from chronic illnesses and from the disabling residual impairments of past diseases whose acute phase the patient has survived. Please note that this astronomical list has not yet included the psychiatric hospital, the psychiatric outpatient department, or the consulting room of the private practitioner. Nor has it included the many administrative and policy functions which the psychiatrist is called upon to fill in medical schools, where he must first help to screen the applicants, and then all too frequently is called upon to treat as well as teach his medical students, and many of his colleagues as well.

All of this means that we are learning to recognize and reluctantly to acknowledge the fact that both the neurotic process and the schizophrenic processes are ubiquitous, if masked and subtle, ingredients in the human psyche; that they are not diseases grafted on us from the outside by special physiological disturbances or by catastrophic events, or even by long-continued stresses; but that they are part of the process by which we develop, something that shadows the entire growth process, and about whose subtler, masked, or subclinical manifestations we still have much to learn, before we will be able so to guide them as to lessen their destructive influence on human life.

I need hardly reassure you that this does not mean that more people are developing neurotic and prepsychotic difficulties. It means only that of the greater number of youngsters who are born more survive; and that survival has become the rule for oldsters as well. This is causing an enormous increase in the number of younger and older people who need either preventive or curative psychotherapy, based upon the most astute and sophisticated psychodiagnoses. Yet this is not minor psychiatry, analogous to "minor surgery." Quite on the contrary, it is major in every sense of the word, i. e., both in volume and in the degree of skill which it requires.

Large additions to this demand arise as a consequence of the fact that all of medicine is passing slowly through a long period of half-cures. Every medical and surgical discipline must go through stages in which it can keep people from dying or from becoming totally disabled, but without restoring them to full health. This is happening today in every aspect of organic medicine and surgery, and in psychiatry itself. We are being challenged on all sides by increasing numbers of human beings who are half-sick and half-well, and who, because of the triumphs of modern medicine, reach old age in that state. The problems which this creates are self-evident: and these patients and their families are being brought to psychiatrists in increasing numbers for psychodiagnosis and psychotherapy. This is a problem which merits a chapter of its own.

Further, increasing attention is being given to the urgent need to prevent psychological derangements. Ultimately, prevention will require a new education. Today, however, prevention depends primarily upon early diagnosis and treatment, for which more men must be trained. Yet the earlier we try to diagnose and treat, the more difficult is the task. This constitutes one of the difficult frontiers of clinical psychiatry —not tasks for beginners or for the half-trained.

Finally, large new areas of the earth are opening up, with new demands for psychiatry. There are states in our own United States which are just now becoming aware of their needs for psychodiagnosis and psychotherapy. The influence of the World Health Organization and of the World Federation of Mental Health is making articulate similar demands from the whole face of the globe.

What I have been saying would seem to imply that if we go about with a modern version of Diogenes' lantern in hand, we

will find psychiatrists busily at work performing all of these varied and miraculous tasks. Actually we all know that this is not the case. What our modern Diogenes will find is that from all human activities arises an increasing and incessant clamor for the psychiatric help which still is not available, simply because there are not enough trained psychiatrists to meet even a minute fraction of this demand. Instead, he would find here and there *one* psychiatrist of varied training giving, at the worst, a demonstration of how *not* to do such work. At the best, he supplies a small sample of how valuable such services might be if only enough trained personnel were on hand. Thereby he creates an impatient demand for more. But since there are no psychiatrists to satisfy the hunger which he has roused, the frustrated claimant turns in anger to the untrained, to the cultist, and to the quack, who will exploit his need. If medicine is ever to meet these needs which our advances have awakened and made articulate, we must train enormous numbers, far more than we have at present. I shall not ask, "Can we do it?"; I shall ask, "How can we do it?"

The United States has more psychiatrists than there are in all the rest of the world. We know that these are not enough. Therefore our first practical question must be, "What are the prospects and chances of increasing their numbers materially?" At present, there are between 8000 and 9000 members of the American Psychiatric Association. Of these, 2500 to 3000 are in administrative posts. About 1000 devote the major part of their time to teaching in medical schools. About 2500 to 3000 are physicians on the full-time staffs of mental hospitals. Thus, out of the original 8000 to 9000, only about 2500 to 3000 are left to service the vital needs of the nonhospitalized population of 170,000,000.[3,4,11] It is variously estimated that to meet adequately the many demands which I have listed, we would need between 25,000 and 50,000, the latter being closer to the true requirements.*

Let us consider where these might come from. (I draw these data from the official statistics of the American Psychiatric Association[2] and of the American Medical Association.[1]) There were 200,000 physicians in this country in 1950; 250,000 is our maximum expectation by 1960. (This may be an overestimate, because it was made at a time when the applications for medical schools were rising, whereas in recent years they have been dropping.)

The official estimate of what this will mean in terms of physicians per 100,000 runs as follows: In 1940, there were 133 doctors per 100,000; in 1960, there will be 143 doctors per 100,000. If this entire increase of 10 per 100,000 were to become psychiatrists, they would not be enough. If another 10 per 100,000 could be diverted from medicine and surgery by greater economies in the use of medical and surgical time, even such an addition could not begin to meet community needs. Simple computation will indicate that the total gain in psychiatric strength which these figures imply is between 2000 and 4000 men.

Moreover, if we are realistic, we will accept the fact that for many valid reasons most doctors prefer to work in strictly medical settings, and that, consequently, not

* Should anyone consider this an extravagant estimate, I would call attention to the fact that in the quarter-century which elapsed between 1930 and 1957 the number of active scientists working in the United States increased by over 200,000, starting from 46,000 (*Science* 125:143 [Jan.] 1957). In this same quarter-century an excessively generous estimate of the increase in the number of psychiatrists, as estimated by the size of the American Psychiatric Association, is under 8000.

Psychiatry involves the lives of everyone, from infancy to the grave, and deals with our most pressing public health problem. Yet the increase in absolute numbers has been about one twenty-fifth of the increase among scientists as a whole. The future increase which I have here projected brings us up only to the point at which science stood 25 years ago. This is hardly an extravagant estimate of our psychodiagnostic and psychotherapeutic needs.

many of these hypothetical additions to our supply of medically trained psychiatrists would actually work in the various nonmedical, social, legal, industrial, and educational agencies which I have cited.

Further relevant considerations are the facts that we graduate about 6000 medical students per year, that the applications for admission to medical schools are dropping and not increasing, that the creation of an entire new medical school, at vast expense, adds only about 100 new physicians to the annual increment. Meanwhile, we lose 1500 to 2000 physicians per year by death and disablement. Consequently, even if we strain every nerve, our total medical manpower can grow only at a snail's pace.

Finally, anyone who deludes himself that these needs can be served by making of each internist his own psychiatrist is indulging in the purest kind of wishful thinking. As I have said, these are the subtlest and toughest of all psychiatric problems both to diagnose and to treat, and they require large amounts of undivided time and attention. Even if the internist or the surgeon had the necessary experience, knowledge, and technique, he would not be able to devote to this work the time it would require without creating a new shortage of available medical and surgical man-hours.

If we give full weight to the consequences of these hard facts, we cannot pretend to ourselves that the medical profession alone will ever be able to supply the needed numbers of men and women, specially trained to do psychodiagnosis and psychotherapy. Unless we find and train other sources of personnel, many hundreds of thousands of human beings whose needs have become articulate through the influence of modern psychiatry will remain untended; and in consequence they will turn to the untrained, to the partially or poorly trained, and to quacks.

Let us then face the fact that it is impossible to train enough medical psychiatrists ever to fill this need, and that if we do not want to yield this basic aspect of human culture by default to the wild and to the untrained, then are we not forced to the conclusion that our medical schools should join forces with the behavioral scientists of our universities to develop a new scientific and medical subdiscipline under a new title, i. e., a Doctorate in Medical Psychology? The practitioners of this profession would never replace the medically trained psychiatrist, but they would supplement his labors; and, if the training is properly organized, they would work shoulder to shoulder with physicians in the service of man's psychological needs. Let me say emphatically that we must aim realistically *not* at filling the gap tomorrow, or even at a five-year plan, but at a 25-year plan, which, however, will begin to yield limited results in 10 to 15 years. It is to such a plan for a solution of this problem that I invite your attention.

It is my contention that the logical, practical, and socially and culturally desirable solution is through the development of a new profession, a Doctorate of Medical Psychology, trained under the joint auspices of medical schools and universities. The doctors of medical psychology would be licensed to practice psychodiagnosis and psychotherapy under legally defined conditions, specifying their relationship to physicians, so that the dangers of overlooking organic disease would be avoided. (The nature of these stipulations will be described in detail below.)

With this general program in mind, let us consider the sources, first of teachers, and then of students, and, finally, the nature of the curriculum for both groups.

I. The Sources and Training of Teachers

Because of the shortage of competent teachers among medically trained psychiatrists, we would have to start by training a new cadre of teachers. Therefore, into the curriculum that I shall describe below it would be necessary at the start to draw a group of men and women who were rec-

ognized for their creative attainments in the behavioral sciences, i. e., trained and experienced in clinical and experimental and social psychology, in psychiatric social work, in remedial and vocational education, and in cultural anthropology. Such trained and mature specialists, of acknowledged scientific and professional stature, would have to be fully subsidized for periods of additional training, varying from 5 to 10 years, so as to turn them into the nucleus of the faculties which would ultimately carry a major share of the burden of training the future practitioners of the new profession.

This first batch of future teachers would come with widely divergent previous training and experience in various aspects of behavioral science. Therefore this initial curriculum would have to be tailored individually to meet each individual's needs in the basic and clinical sciences. The over-all goal of the curriculum would be to develop scientific critique and sophistication, and to deepen and broaden and criticize all previous clinical diagnostic and psychotherapeutic experience. Even in those instances in which this previous experience included many years of psychodiagnosis, psychotherapy, and psychoanalysis, the new curriculum would require close supervision of all forms of psychotherapy, including psychoanalytic psychotherapy, group and individual techniques, hypnotherapeutic techniques, plus the integration of psychological testing with psychotherapy. In launching the clinical training of this initial group, experienced psychiatrists and psychoanalysts would therefore be called upon to give more time than will be necessary in later phases of the program.

Since the goal would be to develop self-critical and skeptical therapists and diagnosticians, such a training program would place major emphasis on the critical dissection of taped recordings, and also of movies of their own therapeutic efforts before group seminars. Thus, the training of this first group of teachers would actually be far more exacting than is the training to which the average medical psychiatrist or psychoanalyst is exposed today in our current postgraduate training programs, whether in medical schools, in psychiatric hospitals, or in psychoanalytic institutes.

In the more general and basic aspects of the training of these future teachers, it would be essential to supplement any deficits in their prior scientific background by including an exacting review of human biology. One could use as a model the curriculum in Basic Medical Sciences at the Harvard Medical School for men who are going into research in human biology. This includes intensive training in the fundamental principles of general physiology, and in particular of neurophysiology, both normal and pathological.

The minimal duration of training for even the most experienced of these future teachers would probably be at least five years; and its over-all duration might be as high in individual instances as 10 years, before they would be ready to establish and maintain the high standards for their future students at which the curriculum would aim.

Among clinical psychologists there will be some objection to the insistence on the importance of so many years of additional training. There is no question that in a few individual instances this would be superfluous, and would work an unnecessary hardship. There is even less question, however, that the possibility of securing wholehearted cooperation from the medical profession and of creating a true partnership between the two disciplines will be enhanced by holding strictly to such a stipulation. Furthermore, we must remember that this is a plan to train a corps of future teachers; and that it takes the medical analyst a minimum of 5 additional years of practical analytic experience after he has fulfilled all training requirements in a curriculum which lasts 12 to 14 years, before he is considered to be eligible for appointment to the faculty of a psychoanalytic institute. Therefore this requirement does not constitute a discrimination against the non-

medical scientist. It merely subjects him to the same high minimal standards as those to which his medical counterpart already conforms.

II. The Sources and Training of Students; General Considerations

(*a*) *Sources.*—Once such a corps of specialized teachers is ready, their students would come to them directly from college, just as men today graduate from college to enter law school, medical school, or engineering school. Prerequisite for admission would be certain basic courses in general science, higher mathematics, statistical methods, sociology, psychology, and anthropology. Here, however, there would be room for many local differences and for the comparison of different approaches, just as there are differences in the requirements for admission to different medical schools. Certainly in this group the humanities would not be slighted.

Unlike the initial cadre of future teachers, this crop of future college graduates would enter upon a more standardized curriculum, in which it would be possible to exact more nearly universal minimal requirements. This would follow the precedent established by our medical schools, law schools, and engineering schools.

But what kinds of college students would be attracted to such a postgraduate professional training program as will be outlined below? The conscious common denominator, of course, would be an interest in human behavior, starting in many instances with his own. It is true, of course, that some might be impelled to train for this new profession for mercenary reasons; but this is also true of the medical profession. And since the new curriculum, as described below, will be a rigorous and lengthy training, we are justified in doubting that the proportion of those whose motivation is preponderantly mercenary would be higher among the doctors of medical psychology than among the doctors of medicine.

Some critics of this plan fear lest the development of a new subdiscipline would seduce many medical students from their medical studies, and from all concern with human biology. These fear that the net effect would be to divorce biology and psychology. Paradoxically, and quite inconsistently, the same critics complain that too many of the students in the curriculum on medical psychology would after a time wish to become physicians. These opposing predictions demonstrate the rather fantastic nature of the fears. Furthermore, there is no way of estimating how valid the prophecies themselves may be. An occasional interchange of students between the two curricula does not seem to be a matter of great moment. It is not likely that there would be an unbalanced interchange, going predominantly in one direction or the other.

Finally, many behavioral scientists are worried lest the new curriculum will drain off into the practice of the new profession all promising research brains. For this fear there is equally little basis. For the many practitioners in any profession, there is only a small group of creative investigators. There is no reason why this should not be equally true of a doctorate in medical psychology, with a constant mutual interchange between the scientist and the practitioner, each feeding facts and problems and stimulus to the other, just as there is in medical science. To provide sound training facilities for the doctor of medical psychology will merely increase the total reservoir of trained men in this field, from among whom research minds recruit themselves. Thus in time a body of adequately trained and matured practitioners would inevitably provide more and better research men in the field of the behavioral sciences. Here it is important to emphasize again that the high level of American medicine, like the high level of American dentistry, is due to the coexistence of its own corps of teachers, practitioners, and researchers. That is the pattern which this plan aims to reproduce in

the behavioral sciences, under the joint auspices of medical schools and universities.

(*b*) *Auspices.*—Of primary importance for the success of this plan is the fact that it would be carried out under the conjoint auspices of the various university departments which deal with the behavioral sciences, together with the medical schools. Administrative problems would be simplified if within the university, for this purpose at least, all of the separate disciplines which contribute to behavioral science could be affiliated in one interdepartmental department (as is done at Harvard in the Department of Social Relations).

(*c*) *The Setting.*—The preclinical parts of the curriculum which are given by the behavioral scientists in the academic divisions of the university could best be given in their own lecture halls and laboratories.

The clinical aspects, however, would be carried on in the physical plant of the affiliated medical school and teaching hospital. There are several reasons why the medical setting and location are important. Since many of the techniques with which the student is to be equipped must be learned in a medical school, it will be economical of space, staff time, and equipment to house these together. Moreover, accessibility to patients and to patients' families is essential to clinical teaching. This, again, requires the medical setting. Even more vital is the fact that everyone who is going to have responsibility for human health should have an opportunity to develop a sense of identification with everyone else who is engaged in any of the healing arts. There could be no medical profession as such, and no bond of mutual understanding and aspiration, if from the start every specialist were trained in a special plant, physically apart from the others. Such a system would spawn groups of competing and mutually distrustful specialists. The fact that we live our student lives together is essential for our later spiritual kinship. For the same reason, the future doctors of medical psychology must share their student years with medical students. Moreover, such daily contacts will gradually and automatically impart many of the traditions of scientific medicine, just as happens to the medical student: such as the sense of dedication to therapeutic goals; a deep and automatic respect for each human being's right to privacy; and, finally, and perhaps most important of all, a tough-minded skepticism about naive, unjustified, and exaggerated therapeutic claims. The physician's hard teacher in these matters has been his experience of centuries of defeat and the repeated facing of his failures at the autopsy table. We can hardly claim that no physician ever forgets these lessons; but we can claim that when he forgets them, the painful experience of failure soon jogs his memory and his scientific conscience. To share in these emotional experiences is as essential a prerequisite to responsibility for diagnosis and for therapy in the psychological field as is the technical and clinical training; because ultimately these lessons must become part of the tradition of a future Doctorate in Medical Psychology. Let me repeat that if he is to share such responsibilities with the physician, the Doctor of Medical Psychology must become spiritually one with the physician and not his rival, and that this can happen only if they study and live together in their student years, so that they can grow up together, work together, succeed, and fail together in the dedicated atmosphere of medical schools and teaching hospitals.

III. The Curriculum

In the various departments of the university, partly in his undergraduate years and partly in the graduate curriculum for a Doctorate in Medical Psychology, the future practitioner of this profession will learn the principles of experimental methodology, of basic chemical, physical, and biological science, of higher mathematics, and of critical statistical methodology; the techniques of experimental psychology and of clinical psychological testing; the techniques and data of child psychology, of comparative and

experimental animal behavior, and of comparative social and cultural anthropology. In medical schools he will learn human biology, both normal and under the influence of disease, and he will learn how to apply to patients all of the general knowledge of behavioral science which he has acquired in the university.

The over-all curriculum, then, would consist of the following components:

A. Preprofessional (undergraduate)

The basic physical and chemical sciences, comparative biology, experimental methodology; the behavioral sciences, including experimental, clinical, social, developmental, and child psychology, cultural anthropology, and primitive psychology; comparative animal psychology and ethology; philology; higher mathematics and statistical methods in general, and the humanities.[8]

B. Professional

1. Preclinical (first and second years)

(*a*) A course in basic medical science (comparable to that now offered in Harvard Medical School to men who want to work in medical research but not in the practice of medicine).

(*b*) Medical and psychiatric sociology (with social case work).

(*c*) Further techniques of psychological testing.

(*d*) Graduate work in the disciplines under *A*, above.

2. Clinical: Prepsychiatric (second and third years)

(*a*) A sense of at-homeness with human beings who are suffering from organic disease is essential for the emotional and intellectual preparation of a future doctor of medical psychology. This is essential also as a comparative basis for a later understanding of human beings who suffer from psychological ailments. Therefore the student would first be exposed to patients on medical and surgical wards of general hospitals, i. e., who are suffering from organic diseases. Here his successive functions would be three: (1) first, as an orderly or nurse's aid, (2) then as a clinical clerk, learning how to gather critically the interdependent story of human lives and of their organic complaints, and (3) administering and scoring psychological tests to such patients.

(*b*) This experience would then be enriched and supplemented by direct contacts with patients and their families in their own homes. The initial contacts would be organized under the general medical social service, subsequent ones under psychiatric social service, in connection with the care both of ward and of outpatient.

In the course of time through such experience on wards, in the outpatient department, and in the home, patients suffering from organic disease, with or without concurrent neuroses and psychoses, would no longer be news to such a student. They would be human beings with whom he had lived and worked for at least two years, experiencing their daily fluctuations in health and illness. In later years when he encounters manifestations of organic disease as complications of psychiatric illness, they will be familiar to him; and he will not neglect them or deny them, because he will not be frightened by their unfamiliarity.

(*c*) Work is continued on a graduate level in the basic disciplines listed above under *A*. Note that there would thus be four years of maturing in the preprofessional or basic disciplines, spotted through the years of professional training.

3. Clinical-Psychiatric (fourth through seventh years)

The third step in training (i. e., probably starting in the fourth year of the professional curriculum) would take the student to the psychiatric division of the hospital and to its psychiatric outpatient department. There he would go through steps in training which would parallel what he had been through on the medical and surgical services: to wit, working first as an attendant, then as a clerical clerk, and then as a psychological tester and psychiatric social worker.

Thus every phase through which the student passes would include training in interviewing, in taking life histories, in subjecting patients to psychological tests, in the evaluation of these tests, and, above all, in observing and in understanding the incessant subtle interplay among patients, and among patients, attendants, nurses, and therapists.

4. Psychodiagnostic and Psychotherapeutic (fifth year and on)

The definitive training in psychodiagnosis and in psychotherapeutic techniques would thus be based upon a wealth of diversified clinical experiences on wards, in outpatient clinics, and in homes. Here, as in the training of the initial cadre of teachers, the study of tape recordings and of sound films of diagnostic and of therapeutic interviews would play a major role, with additional opportunities to observe therapeutic interviews through one-way screens, to study filmed interviews, and to participate in seminars based on week-by-week reports and data from the treatment of patients, as conducted both by experienced therapists and by other students.

These steps would lead to the conduct of psychotherapy under supervision, which, in turn, would be subjected to the same rigorous challenge of critical group discussion.

5. For many the final step would be psychoanalytic training. For all there would be training in such special techniques as the use of hypnotherapy and methods of group psychotherapy.

These are the bare bones of the curriculum, the details of which would have to be worked out in actual practice. The total curriculum would take somewhere between seven and nine years after graduation from college, thus saving five to seven years from the time it now takes to train a medical psychiatrist. This means that for any fixed period of time the same training facilities could be turning out almost twice as many graduates as they do now, in addition to the medical psychiatrists who would be in training concurrently.

I must remind you that this increased yield in trained personnel would not start today or tomorrow; but that it would begin to make itself felt in the community as a whole in a minimum of 15 years. From that time on, it would snowball steadily.

IV. Licensure

Neither in law nor in medicine does graduation from a professional school give the right to practice. This right is conferred by the states on the basis of examinations which lead to the granting of a license. Therefore on top of the curriculum which has been outlined, there would have to be a system of examination for licensure, under the control of the various states and/or of a national board. The examining boards would consist of representatives of the behavioral sciences, the basic medical sciences, and psychiatry. Many examiners would be drawn from the original teaching corps in the Doctorate in Medical Psychology.

The license itself could be formulated and granted under terms which would stipulate clearly the conditions of practice, any violation of which would cost the individual his license. For example, it could stipulate that pari passu with the process of psychological examination, and before any regimen of psychotherapy was instituted, every prospective patient must be subjected to a complete physical check-up by a diplomate in internal medicine or pediatrics (depending on the patient's age), who, as needed, would call upon diplomates of appropriate specialty boards. It could stipulate further that such examinations be repeated at regularly prescribed intervals throughout the course of psychotherapy, and again at its termination or interruption. This would provide even better protection against the danger of overlooking organic disease than does our present system.

I must add that there are problems which would still have to be worked out, such as, for instance, the handling of the commitment of patients to mental hospitals when needed, and the use of simple medications (e. g., for sleep, etc.). These details would have to be solved in connection with the licensing procedure, so as to ensure the harmonious integration of the Doctorate in Medical Psychology with the medical profession in the handling of every patient. Certain suggestions concerning these details have been advanced on another occasion.[7]

Finally let me plead that such a plan as this can best be explored not by endless discussion but by several carefully conducted pilot tests, under the auspices of some of our major universities and medical schools, and on small and hand-picked groups of advanced students.

I believe that such tests would soon demonstrate that the gains of such a system would be not solely practical, but that, in addition, many scientific values would accrue from the institution of such a plan. These more general values will be touched on briefly in the final section of this paper.

V. Cultural Values of This Plan

It is true that the practical values which would accrue from this plan are literally essential. Nevertheless, I would not leave the erroneous impression that my interest in this is only because it is a practical method of breaking the bottleneck in trained personnel. Its full cultural implications go far beyond this goal.

It is a truism that man has been able to change almost everything in the world except himself. All of our learning about the outside world has not changed us. Psycho-

analytic psychiatry, however, now gives us a tool, frail and imperfect though it is, which for the first time in human history provides the possibility of changing and advancing man himself, not by changing human nature as such, but quite specifically by shifting the balance of power in human personality out of the hands of a rigid and destructive alliance between unconscious and preconscious processes and into the hands of a far more creative and flexible alliance of preconscious with conscious purposes and critiques.[5,6,8-10] But if we are to achieve the goal which psychoanalytic psychiatry makes it possible at least to envisage, then all cultural influences and institutions must become infused with knowledge that can be gained only from the study of the lessons of illness.

For in psychology, as in all of medicine, illness is the ultimate teacher. This is the deeper significance of the preoccupation with illness, which characterizes modern art and literature. The same principle applies to every unsolved behavioral problem which confronts mankind, whether in economics and government, in the organization and mores of the family, in the problems of marriage and divorce, in the methods by which we bring up our children and the methods by which we educate them. Self-knowledge in depth has been the forgotten man of our culture; and self-knowledge in depth derives from an understanding of the roots of illness which are buried in the depths of every personality. It is this knowledge which must become the common property of all cultural and educational forces: the humanities, the behavioral sciences, general science; indeed, everything we think of as higher education. This implies that direct knowledge of the nature of the neurotic process is the essential ingredient which must now be added to the cultural heritage which each generation transmits to its successors. This knowledge cannot remain the exclusive domain of medicine and of medical psychiatry if our culture is ever to achieve and re-create maturity. This is knowledge which must be brought out of the isolation of the clinic into general currency. And this can happen only if those who are trained in other disciplines are given an opportunity to work at our side to achieve sophistication about psychiatry and the psychology of the neuroses, to carry back into their own disciplines.

Nowhere is this more essential than in the study of the educational process itself, where one can observe the tangled interweaving of the processes of learning with the neurotic process, through the imperceptible gradations betwen the repetitive drill of the learning process and the automatic and involuntary repetitions of the neurotic process. At every level of education from the kindergarten to the highest levels of postgraduate study, educational procedures are a tangled net of normal and neurotic mechanisms. People talk glibly of neuroses as a kind of mal-education and of psychotherapy as a learning process. These are oversimplifications; but it is true that one cannot dissociate the two. Therapy and learning constitute together a joint field for education and psychiatry. They are complementary and inseparable; and the challenge of education itself should free us of any smug idea that psychodiagnosis and psychotherapy can be reserved for the psychiatrist.

This in brief is the broader philosophical basis for my argument. Just as psychiatry left the lunatic asylum years ago, so psychopathology as a discipline, as a theoretical system, as a field of understanding, and as a technique of exploration, must escape the confines of the medical clinic and merge with human culture. This is the cultural voyage of exploration to which this new discipline would make an essential contribution.

7½ East 81st St. (28).

REFERENCES

1. The Alleged Shortage of Physicians, J. A. M. A. Editorial, 142:111-113, 1950.

2. American Psychiatric Association: The Psychiatrist—His Training and Development, Report of the 1952 Conference on Psychiatric Education, held at Cornell University, Ithaca, N. Y., June, 1952, edited by J. C. Whitehorn, Baltimore, The Baltimore Press, 1953.

3. Deutsch, A.: The Mentally Ill in America: A History of Their Care and Treatment from Colonial Times, New York, Columbia University Press, 1946.

4. Gorman, M.: Every Other Bed, Cleveland and New York, World Publishing Company, 1956.

5. Kubie, L. S.: The Problem of Maturity in Psychiatric Research, J. M. Educ. 28:11-27, 1953.

6. Kubie, L. S.: The Fundamental Nature of the Distinction Between Normality and Neurosis, Psychoanalyt. Quart. 23:167-204, 1954.

7. Kubie, L. S.: The Pros and Cons of a New Profession: A Doctorate in Medical Psychology, Texas Rep. Biol. & Med. 12:125-170, 1954.

8. Kubie, L. S.: Freud's Legacy to Human Freedom (Freud Centenary Lecture, May 6, 1956, New York Academy of Medicine, before the Rudolph Virchow Society), in Perspectives, Vol. 1, Sept., 1957; J. Indian Med. to be published.

9. Kubie, L. S.: Impact of Behavioral Medicine on the Preprofessional Education of the Physician, conference on PreProfessional Education for Medicine, under the auspices of the State University of New York, Downstate Medical Center, College of Medicine, Brooklyn, Oct. 18, 1956; to be published.

10. Kubie, L. S.: Vulnerability of the Creative Process to Neurotic Distortion, The Porter Lectures for 1957, under the auspices of the University of Kansas School of Medicine, Lawrence-Kansas City, to be published.

11. National Health Education Committee, Inc.: Facts on the Major Killing and Crippling Diseases in the United States Today, New York, The Albert and Mary Lasker Foundation, 1955, privately distributed.

Reliability of Epinephrine-Methacholine (Mecholyl) Testing

R. BRUCE SLOANE, M.D., Montreal, Canada; DAVID J. LEWIS, M.D., Toronto, Canada, and PATRICK SLATER, M.A., London, England

Autonomic nervous system studies have engaged the attention of psychiatric research workers since the early publications of Eppinger and Hess.[1] However, conflicting results and interpretations reveal the doubt and uncertainty that still lie in this field. Differences of technique and samples are frequently overlooked or minimized and undoubtedly account for much of the existing controversy.

The work to be described was an effort to study the reliability of various methods of performing the epinephrine-methacholine (Mecholyl) test described by Funkenstein and his co-workers.[2]

We commenced first with a series of test-retest comparisons of the responses to the two drugs separately under slightly differing conditions. The comparisons were made in terms of 11 variables—3 involving basal levels of blood pressure; 2, the extent and duration of response to epinephrine, and 6, the description of the methacholine-response curve. Systolic pressures were used at all times.

After the evaluation of the individual drug responses, we describe the effect upon reliability of making injections of both drugs on the same day, of reversing the order of drugs, and, finally, of a preceding injection of epinephrine on the methacholine response.

We also tested the effect of using a dose of 0.025 mg. of epinephrine, which is safer than the 0.05 mg. of epinephrine formerly used. It seemed useful to determine how the recording personnel might affect the administration of the test, and we divided our results according to whether the test was carried out by the same nurse on both occasions or by different nurses. These varying procedures give an idea of the extent to which the test is subject to the conditions of administration.

Material and Procedures

Subjects.—The subjects used in this work were inpatients of the Bethlem Royal and the Maudsley Hospital. There was a total of 111 patients—52 male and 59 female, ranging in age from 16 to 69 years and having a mean age of 39.6 years. The diagnoses were as follows: manic-depressive reactions, depressive state, 53; involutional psychoses, 5; schizophrenia, 18; schizoaffective psychoses, 6; neuroses and character disorders, 28; organic dementia, 1. Three hundred ten comparisons were made. A high proportion of these tests were carried out either before or after E. C. T. but none during the administration of this or any other physical treatment. Cases receiving tranquilizing drugs were excluded. Retests were performed within one week, usually on succeeding days, and if there was intervening clinical change the subject was rejected.

Methods.—Test situation: The patients were tested in single rooms or quieted wards, and all tests were carried out by ward nurses previously instructed in the technique and procedure. No attempt was made to alter room temperature, but patients were kept warmly covered with blankets. The patients had been fasting overnight and were recumbent for a minimum of half an hour before

Submitted for publication March 13, 1957.

From the Bethlem Royal and Maudsley Hospitals, and the Institute of Psychiatry, University of London. This work was carried out while Dr. Lewis held a Travelling Fellowship from the R. Samuel McLaughlin Foundation, Toronto, Canada.

Present addresses: The Allan Memorial Institute of Psychiatry, McGill University, Faculty of Medicine, Montreal, Canada (Dr. Sloane). The University of Toronto, Faculty of Medicine, Department of Psychiatry, (Dr. Lewis). The Institute of Psychiatry, University of London (Mr. Slater).

TABLE 1.—*Blood Pressure Response Variables to Epinephrine and Methacholine (Mecholyl)*

Variable No.	Description	Units
1	Basal blood pressure: mean of last 5 readings within a range of 8	Millimeters Hg
2	Initial blood pressure reading on commencing test	Millimeters Hg
3	Differences between initial and basal readings (Variable 2-Variable 1)	Millimeters Hg
4	Maximal height of epinephrine rise above basal	Millimeters Hg
5	Time for pressure to return to basal after epinephrine	Minutes
6	Maximal fall after methacholine	Millimeters Hg
7	Time to post methacholine homeostasis *	Minutes
8	Area† of fall to methacholine before homeostasis	Area units
9	Total area of fall to methacholine	Area units
10	Total area of rise to methacholine	Area units
11	Maximal rise to methacholine	Millimeters Hg
12	Concordance of blood pressure groupings	Percentage
13	Concordance of prognostic predictions	Percentage

* Homeostasis was defined as the point at which the blood pressure returned to the basal level, or within 4 mm. Hg of the basal level after the initial fall, and remained there for three consecutive minutes. If the blood pressure remained at the basal level for four minutes with one reading outside the range, it was also scored as homeostasis in our series.

† Area was derived by plotting the methacholine curve on graph paper, with the vertical side of each square representing 6 mm. Hg and the horizontal one minute of time.

testing commenced. All tests were carried out between 8 a. m. and 12 noon, and on the same arm.

Technique for Sphygmomanometric Recording: This has been fully described previously.[8]

Dosage: Epinephrine U. S. P. (synthetic) was given intravenously by the physician in a dose of 0.025 or 0.05 mg. Methacholine chloride U. S. P., 10 mg., was given intramuscularly by the nurse.

Scoring: Funkenstein and his co-workers divided the types of systolic blood pressure response to epinephrine and methacholine into six groups. A seventh group was formed by those persons who reacted to methacholine with a chill. Concordance of two tests by this method of grouping is shown as Variable 12 (Table 2), while concordance of prognostic prediction with respect to E. C. T. is shown as Variable 13.

Although these arbitrary groups are the basis of most clinical use of this test, Funkenstein also described seven mathematical measures which could be used to quantify the blood pressure responses. These were obtained from the basal blood pressure, the epinephrine rise, and the methacholine fall. They are shown in Table 1 as Variables 1, 4, 5, 6, 7, and 8. In some cases there was a further considerable fall of blood pressure after homeostasis, and to include these we introduced Variable 9. In yet others there was a compensatory, or even initial, rise of pressure to methacholine, and this was expressed as Variables 10 and 11. We were also interested in testing whether it might be unnecessary to take a basal reading and so included the initial blood pressure (the first reading taken after the period of rest) as Variable 2, and the difference between this and the basal reading as Variable 3.

Results

In Table 2 the test-retest correlations for each of the mathematical variables are shown in lettered horizontal rows according to the technique used.

Basal Blood Pressure.—Variable 1: The basal blood pressure showed a rather high reliability in all the methods tested, with one exception, namely, when methacholine preceded epinephrine on the same day (Row L). Generally the reliability was between 0.6 and 0.95. This meant that a second basal reading could be predicted from the first with between 40% and 90% of accuracy.

Variable 2: Initial blood pressure readings correlated somewhat less well, being usually only 0.1 below the basal but sometimes showing marked irregularity.

Variable 3: This variable, which indicated the relationship between the basal and the initial blood pressure, showed an invariably poor reliability. From this it is clear that not only was there no relationship between the two measures but also that Variable 2 could not be used even for a test independent of basal blood pressure because it was too unreliable.

Epinephrine Administration (Rows A, B, and C).—Three series were compared which showed the epinephrine responses when the drug was given alone on both occasions or when it was given as the first drug of the day.

Variable 4 (height of epinephrine rise): The response to the injection of 0.05 mg. of epinephrine when recorded by the same nurse appeared highly reliable. When the recording was done by different nurses, however, the reliability fell to an insignificant figure. It was also very low when a smaller dose of epinephrine was given, even though the recording was done by the same nurse.

Variable 5 (duration of epinephrine response): This value showed poor reliability.

TABLE 2.—*Test-Retest Correlations for Seven Mathematical Measures of Blood Pressure Responses to Epinephrine and Methacholine*

Rows	Drug	Dose, Mg.	Technique	Observer	No. of Comparisons	1 Basal B. P. Mm. Hg	2 Initial B. P. Mm.	3 Difference Between Initial and Basal B. P., Mm.	4 Maximum Epinephrine Rise, Mm.	5 Duration of Epinephrine Rise, Mm.	6 Maximum Fall Methacholine, Mm.	7 Duration of Fall, Min.	8 Area of Fall to Homeostasis, Units	9 Total Area to Fall, Units	10 Area of Rise Rise to Mecholyl, Units	11 Maximum Rise to Methacholine, Mm.	12 Concordance of Grouping	13 Concordance of Prognostic Prediction
A	Epin.	0.05	Given alone on separate days	Same	23	0.652	0.764	—0.176	0.836	0.580								
	Cf. Epin.	0.05																
B	Epin.	0.05	As above	Different	17	0.792	0.287	0.428	0.482	—0.261								
	Cf. Epin.	0.05																
C	Epin.	0.025	As above	Same	30	0.954	0.860	0.065	0.194	0.206								
	Cf. Epin.	0.025																
D	Epin.	0.025	As above	Same	16	0.941	0.807	0.445	0.762	0.024								
	Cf. Epin.	0.05																
E	Epin.	0.05	As above	Same	12	0.879	0.641	0.096	0.572	—0.261								
	Cf. Epin.	0.025																
F	Meth.	10	As above	Same	31	0.776		0.080			0.727	0.607	0.710	0.697	0.662	0.774	77%	90%
	Cf. Meth.	10																
G	Meth.	10	As above	Different	15	0.921		—0.217			0.819	0.446	0.750	0.798	0.474	0.125	47%	67%
	Cf. Meth.	10																
H	Epin.	0.05 + 0.025	As above	Same	7	0.949	0.988	0.660	0.637	—0.158	0.872	0.738	0.791	0.785	0.861	0.852	100%	100%
	Meth.	10 mg.	As above															
	Cf. Epin.	0.05 + 0.025	As above															
	Meth.	10	As above															
I	Epin.	0.05	Epin. preceding meth. on one day	Same	9	0.652	0.560	0.118	0.885	0.708	0.429	0.416	0.464	0.522	—0.275	—0.209	11%	44%
	Meth.	10																
	Epin.	0.05	Epin. preceding meth. on another day															
	Meth.	10																
J	Epin.	0.05	Epin. preceding meth. on one day	Different	39	0.654	0.582	0.153	0.424	0.144	0.106	0.147	0.220	0.214	0.032	0.134	33%	67%
	Meth.	10																
	Cf. Epin.	0.05	Epin. preceding meth. on another day															
	Meth.	10																
K	Epin.	0.025	As above	Same	17	0.954			0.404	0.358	0.787	0.431	0.648	0.651	0.349	0.383	59%	71%
	Meth.	10																
	Cf. Epin.	0.025	As above															
	Meth.	10																
L	Meth.	10	Meth. preceding epin. on one day	Same and different	11	0.338	0.596	0.138	0.346	0.598	0.620	—0.165	0.334	0.217	0.288	0.448	90%	100%
	Epin.	0.025																
	Cf. Meth.	10	Meth. preceding epin. on another day															
	Epin.	0.025																
M	Epin.	0.05	Epin. preceding meth. on one day	Same and different	7	0.874	0.824	—0.374	0.610	0.293	0.016	0.452	0.309	0.287	—0.202	0.382	57%	86%
	Meth.	10																
	Cf. Meth.	10	Meth. preceding epin. on another day															
	Epin.	0.05																
N	Meth.	10	Alone on one day	Same and different	52	0.708	..	0.055	..		0.532	0.159	0.460	0.438	0.625	0.510	46%	83%
	Cf. Meth.	10	Following 0.05 mg. epin. on another day															
O	Meth.	10	Alone on one day	Same and different	24	0.846	..	0.340	..		0.527	0.364	0.663	0.662	0.112	0.325	37%	83%
	Cf. Meth.	10	Following 0.025 mg. epin. on another day															

Again, the correlation with the same nurse recording was higher.

Comparison of Unequal Doses of Epinephrine (Rows D and E).—When 0.025 mg. of epinephrine was given on the first day and 0.05 mg. on a subsequent occasion, the reliability was comparable, in Variable 4 (height of epinephrine rise), with that obtained when 0.05 mg. was given on both occasions. When the larger dose was given on the first occasion, the reliability was considerably less. Variable 5, the duration of the epinephrine reaction, showed a poor correlation by either technique.

Methacholine Injection Alone (Rows F and G).—The correlations when this drug was administered alone were between 0.6 and 0.8. There was much greater uniformity than with the epinephrine correlations throughout. The loss when the work was done by different nurses was not so great, some correlations being actually a little higher under these circumstances. The poorest correlation obtained was that which measured the height of blood pressure rise after the establishment of homeostasis.

The prediction level attained with this test when done under optimal conditions suggests that a 50% prediction of a second reading can be made from a first. Agreement among arbitrary groups was 80%, and that for prognostic predictions, 90%.

Epinephrine and Methacholine on Separate Days (Row H).—Our material did not permit us to examine more than seven cases in which epinephrine was given on one day, methacholine on a second, epinephrine again on a third, and methacholine for the second time on a fourth, and final, day. These cases, too, were divided among cases in which 0.025 and 0.05 mg. of epinephrine were given, there being three of the former and four of the latter. This short series provided the most consistently reliable correlations that we found. Examination of the epinephrine scores again showed that the 0.05 mg. dose was more reliable. Better results in Variables 4 and 5 could be expected if all the cases were executed with that dose. Agreement among arbitrary groups (Variable 12) and for prognostic predictions (Variable 13) was 100%.

Epinephrine Followed by Methacholine on the Same Day (Rows I, J, and K).—A large proportion of our tests were carried out on the same day, epinephrine being given first in a 0.025 or a 0.05 mg. dose, followed by methacholine after an interval of 15 minutes to ½ hour, when the blood pressure had returned to the basal level. Tests of this nature appeared to be less reliable. Again, the effect of a different blood pressure recorder was to lower accuracy. In the 39 cases done by different recorders (Row J) the correlation for methacholine Variables (6 to 11) was vanishingly small (0.03 to 0.22).

If the smaller dose of epinephrine was given, the disruption of the methacholine correlations was not so great (Row K). Variables 6, 8, and 9 were close to the best obtained, but the others were poorer. Concordance of groupings and prognostic predictions was also somewhat better than when the larger dose was given. However, the epinephrine variables also showed low reliability.

Methacholine First, Epinephrine Second, on Same Day (Row L).—Reliability was low. Since this test series was carried out by the same nurses in most cases (10 out of 11), one would have expected to obtain somewhat higher correlations, particularly in the methacholine variables, which should have been comparable to those done on separate days (viz., Row F). The epinephrine correlations were also low, but not much lower than those found when the test was carried out in reverse order, that is, with epinephrine as the first drug and methacholine following.

Although the mathematical variables showed these poor correlations, it will be noted that there was almost complete agreement among the arbitrary groups, and that prognostic agreement was complete. This, then, may be a very practical way of carrying out the test, and it deserves further

study in a longer series, in which the effect of chance upon the distribution would be somewhat less.

Epinephrine Followed by Methacholine on Same Day with Methacholine Followed by Epinephrine on Another Day (Row M).—When the test was carried out in this manner, correlations appeared to be a little better than when epinephrine was given as the first drug on both occasions. Methacholine variables and the arbitrary groups again showed poor results.

Methacholine Administered Alone Compared with Methacholine Following Epinephrine (either 0.025 or 0.05 mg.) (Rows N and O).—Again, the disorganizing effect of a preceding injection of epinephrine was shown in the lowered correlations, groupings, and prognostic predictions, compared with those obtained from methacholine given alone on two separate occasions (Rows F and G). However, the effect of the larger dose of epinephrine was less marked in this series.

Reliability of Sphygmomanometry.—In order to check upon the internal reliability of blood pressure readings, we carried out an epinephrine-methacholine test using four observers instead of one. Those participating were two nurses with a great deal of experience in our research work, a nurse with only limited experience, and a physician. A single sphygmomanometer was applied on one arm of the patient, and a stethoscope with four ear appliances was attached over the brachial artery.

Each observer made readings on each of the insufflations. If in doubt, they were instructed not to record, and on an average 2 readings in 50 were so missed. The test was carried out in such a way that one observer had no opportunity of comparing readings with the others, and no corrections were made.

There were 60 readings for each observer, and the standard deviation of the readings about the mean was ±3.4 mm. Hg. Correlation among observers was 0.94, but to some extent this high figure was an artifact of wide range of blood pressures induced by the injection of epinephrine and methacholine. (Thus the maximum pressure recorded was 167 mm. Hg, and the minimum 114 mm. Hg, yielding a mean of 133.5 mm. and a standard deviation of ±18.6.)

In view of technical difficulties, such as attenuation of sound in the long tube, this correlation was encouragingly high. Although the procedure neglected the influence of different insufflators, it gave some indication of the accuracy of the method.

Conclusions

There was a fair test-retest reliability of blood pressure responses to epinephrine and methacholine. This was raised if the drugs were given on separate days and lowered if one drug preceded another on the same day, even though time was allowed for apparent stabilization of the blood pressure between injections. As might be expected, in almost all cases, the correlations were higher when the two tests were carried out by the same observer. This was probably due to differences of technique more than to personality, although the latter undoubtedly played a role.

While estimation of the resting basal blood pressure could be achieved with good reliability (0.65 to 0.95), the initial blood pressure gave low and erratic correlations, and there appeared to be no constant relationship between the two pressures. Thus, the initial reading could be used neither as a datum point nor as a method of estimating the basal reading.

A dose of 0.05 mg. of epinephrine gave a more reliable rise of blood pressure than 0.025 mg., but also had a more disturbing effect on the methacholine variables if this part of the test followed on the same day. There was a tendency for a slight increase in height of response to occur when second doses of epinephrine were given. Duration of epinephrine rise to either dose showed poor reliability.

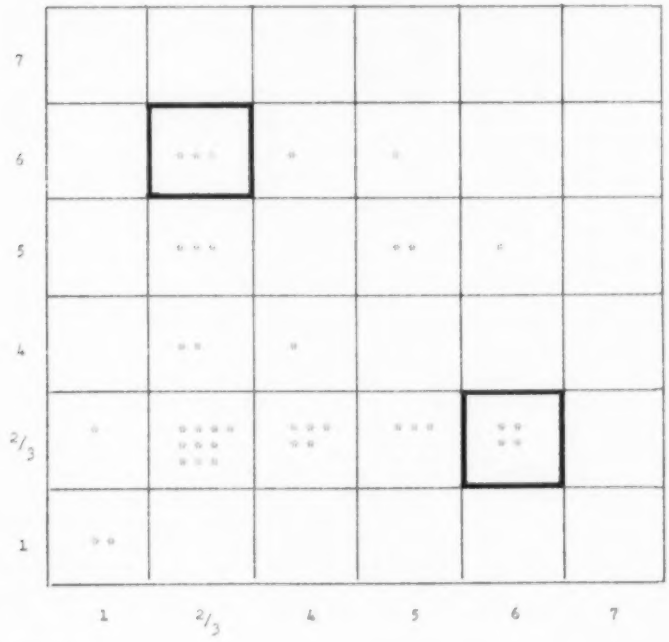
Methacholine responses were reasonably reliable (from 0.6 to 0.8) when not preceded by another drug on the same day. As

increasingly stronger doses of epinephrine were given in the period before the methacholine injection, the correlations fell to very low levels.

Comment

Epinephrine has, of course, a well-known diphasic action on the circulation. A phase of hypotension succeeds the pressor response, and the drug has been shown to have both inhibitory and excitatory properties. However, only two of a series of 25 patients showed a lower blood pressure than their resting level 25 minutes after injection of 0.05 mg. of epinephrine intravenously. Nevertheless, from our results it was clear that epinephrine disrupted homeostasis, so that subsequent administration of methacholine resulted in unpredictable responses on different occasions. Possibly the prior administration of any drug affecting the autonomic nervous system on the same day would have a similar disruptive effect. Weckowicz [4] recently reported upon 20 methacholine retests done in the evening of the same day. Although he claimed "quite a high reliability" for the test, he excluded from his comparison five of the subjects who showed a different response on the two occasions. Had these been included, his correlations would have been greatly lowered, and this result may have been contributed to by the technique, even though the two tests were separated by hours.

For prognostic purposes Variables 6, 7, 8, and 9, which were concerned with the methacholine fall, were the most valuable, and the reliability of these measures fell considerably after epinephrine. However, since the blood pressure response was expressed in wave form and these variables indicated the shape of the wave, it did not seem essential to demand equal reliability between measures at all points on the curve for the technique to be valid. This assumption was borne out by our results,[3] showing that prognostic predictions from the one-day test were not dissimilar from those of two-day tests, despite the considerably lower reliability of the former. Thus, in the series



Scattergram of test-retest results in 39 cases in which 0.05 mg. of epinephrine preceded 10 mg. of methacholine on the same day.

where the larger dose of epinephrine preceded methacholine and the two tests were performed by different nurses, the correlations of the methacholine variables were the lowest obtained, but the misclassification between the so-called "good" and the so-called "bad" prognostic group was less than expected, namely, 7 out of 39 (Figure). Thus the test had some prognostic validity despite relatively low reliability. However, in terms of practical application, it seemed that if these drugs were to be used as a prognostic test they should preferably be given on separate days.

Summary

The reliability of epinephrine-methacholine (Mecholyl) testing and the influence of various techniques of administration were assessed by test-retest correlations.

When methacholine was given alone or as the first drug of the day, correlations of the blood pressure fall were fair (varying from 0.6 to 0.77). There is a moderate amount of misclassification into Funkenstein's arbitrary groups but a good degree of prognostic concordance of the two tests.

Prior administration of epinephrine greatly reduced the reliability of the methacholine variables and arbitrary grouping, and the higher the dose the greater the disruption. As might be expected, reliability was greater when the same observer carried out both tests.

These results suggest that for prognostic purposes the drugs should be administered on separate days, or methacholine given alone. If epinephrine is given on the same day, it should follow, and not precede, methacholine.

Prof. Aubrey J. Lewis gave advice and encouragement; doctors on the hospital staffs allowed us to test their patients; nurses participated in the study, and the research committee of the Board of Governors of the Bethlem Royal and Maudsley Hospitals gave financial assistance.

Allan Memorial Institute of Psychiatry, 1025 Pine Ave. West.

REFERENCES

1. Eppinger, H., and Hess, L.: Vagotonia: Clinical Studies in Vegetative Neurology, Ed. 2, authorized translation by W. M. Kraus, and S. E. Jelliffe, New York, Nervous and Mental Disease Publishing Company, 1917.

2. Funkenstein, D. H.; Greenblatt, M., and Solomon, H. C.: Prognostic Tests Indicating the Effectiveness of Psychiatric Treatment, A. Res. Nerv. & Ment. Dis., Proc. (1951) 31:245, 1953.

3. Sloane, R. B., and Lewis, D. J.: Prognostic Value of Adrenaline and Mecholyl Responses in Electroconvulsive Therapy, J. Psychosom. Res. 1: 273, 1956.

4. Weckowicz, T. E.: Reliability of the Mecholyl Test, A. M. A. Arch. Neurol. & Psychiat. 76:109, 1956.

Depressive and Paranoid Reactions

Application of Adaptational Principles to Their Understanding

CHARLES E. ORBACH, Ph.D., and IRVING BIEBER, M.D., New York

The Section of Research Psychiatry at Sloan-Kettering Institute and the Neuropsychiatric Service at Memorial Hospital have conducted studies of patients who have undergone abdominoperineal resection,[9] radical mastectomy,[2] total gastrectomy, or hysterectomy,[5] to identify the psychological problems associated with cancer and specific surgical procedures. The major purposes of these investigations were to determine the measures which could be employed (1) to reduce the incidence and severity of postoperative hypochondriasis with associated curtailment of activity, and (2) to provide a rationale for the establishment of a rehabilitation program for patients with cancer.

During the course of research with the above objectives the development of major psychiatric disorders other than hypochondriacal reactions has been observed. Depressive and paranoid reactions have been observed where there was no evidence of their prior occurrence in such form. This development does not imply, however, that the potential for psychopathology was not present, or even manifest in certain patterns of thinking and feeling. The depressive and paranoid reactions observed frequently appeared simultaneously or occurred during different phases of treatment in the same patients. There has also been an opportunity to confirm these observations in our contact with patients referred for specific management problems or for psychiatric evaluation. Many of the latter patients have been as intensively studied as those included in the controlled investigations.

Submitted for publication March 25, 1957.

From the Section of Research Psychiatry, Sloan-Kettering Institute, and the Neuropsychiatric Service, Memorial Hospital, Memorial Center for Cancer and Allied Diseases.

Consultant in Clinical Psychology, Department of Home Care, Division of Social Medicine, Montefiore Hospital (Dr. Orbach). Research Psychiatrist, Section of Research Psychiatry, Sloan-Kettering Institute, and the Neuropsychiatric Service, Memorial Hospital, Memorial Center for Cancer and Allied Diseases (Dr. Bieber).

Composition of the Study Group

The entire group, which will be discussed in this report, except for a few cases, were clinic patients at Memorial Center. Although such a group at Memorial Hospital contains many persons of a higher socioeconomic level than would be found in a clinic population in other major New York hospitals, the average occupational and educational level is lower than that of a private patient population. The largest ethnic and religious group in the total sample is composed of first-generation Eastern European Jews. The exact composition of the samples in the colostomy and mastectomy investigations, which were utilized in this study also, is reported in detail in previous publications.[2,9] The other important characteristic of the sample is that it is not drawn from a psychiatric population. The entire range of human adaptation, from extremely well-integrated persons to noninstitutionalized psychotics, is represented in the patient population at Memorial Hospital. In fact, a high proportion of patients available for psychological study can be regarded as "normal" by ordinary community standards.

Theoretical Orientation

Research in a hospital which treats serious somatic disease provides an opportunity for

observing the integrative thinking and behavioral processes by which people attempt to cope with threats to their survival, integrity, and acceptability to other people. In addition, the disruptive effects of these threats upon the patient's adaptive techniques promote the direct communication of many basic beliefs and expectancies underlying behavior.

Cognitive processes are attributed such an important role in our conceptualization of adaptation to illness and its treatment that some further elaboration of the nature and function of beliefs and assumptions is necessary. Beliefs and assumptions are the distillates of antecedent experience, the organization of past experience, both personal and collective, into cognitive guides for future action. They may be nonreportable or unformulated, though our experience at Memorial Center has indicated that many are formulated and fully reportable, since they are the products of childhood indoctrination in familial and community conceptions about disease, health, and medical treatment. Cantril and associates [4] have discussed the same concepts in terms with which we are in considerable agreement except for their heavy emphasis upon the nonreportable and noncognitive aspects of man's assumptive world:

> Man builds up his assumptive or form world largely in an unconscious nonintellectual way, in the process of adjustment and development as he goes about the business of life; that is, as he tries to act effectively to achieve his purposes (page 196) . . . Because man inevitably builds up for himself an assumptive world in carrying out his purposive activities, the world he is related to, the world he sees, the world he is operating on and the world that is operating on him is the result of a transactional process in which man himself plays an active role. Man carries out his activities in the midst of concrete events which themselves delimit the significances he must deal with.
>
> In the process man is himself changed in greater or lesser degree by having his own assumptive world changed through confirmation or denial as a result of action (page 205).

Action based upon beliefs and assumptions is dependent upon their prognostic reliability, that is, whether or not they function adequately as guides to action. When they are fundamentally challenged by events, so that confidence in their prognostic reliability can no longer be maintained, the constellation of action patterns derived from them becomes disturbed. This disruption of techniques of mastery results in a variety of reactions, such as the depressive and paranoid ones which will be discussed.

A hospital engaged in active cancer treatment, therefore, offers a "laboratory" type of situation for the investigation of complex processes involved in the elaboration of psychiatric disorders. Psychologic reactions can be intensively studied as patients attempt to integrate a sequence of serious threats involved in diagnosis and treatment. At the time of diagnosis the patient is exposed to the possibility of knowing that he has cancer, a disease often regarded by the community as repellent, ravaging, and invariably fatal. Data reported by Abrams and Finesinger [1] support this interpretation of the significance of cancer to patients, particularly the repellent connotations. They found that the most significant and characteristic concept held by a group of 60 patients was that cancer was a disease of unclean origin and repellent to other people.

Although all diseases threatening life are capable of producing disruptive reactions in patients, the specific connotations of cancer tend to increase their appearance quantitatively and probably contribute unique qualitative aspects to the reactions. The threat to survival is undoubtedly an extremely important factor in the emotional reactions of patients with cancer throughout treatment and, in some instances, during their entire lives. However, previous studies at Memorial Hospital indicate that other factors are very significant in the psychologic reactions of the cancer patient. Two factors have been identified as having an important role in the production of depressive, paranoid, and hypochondriacal reactions: (1) the threat posed by disease to the patient's long-term psychologic techniques for preserving health and integrity, and (2) the disruption of his

techniques for maintaining interpersonal relationships. It is with the elaboration of these factors that our present report is essentially concerned.

Techniques for Achieving Acceptability

All humans have the biosocial need to be acceptable to other humans. The term "acceptability" as used in this paper implies the coming of one individual into a positive relation with another. The relationship described as positive is characterized by the presence of one or more of the following attributes: (1) affectionate, affective responses; (2) utilization of the resources of the accepting person for the constructive development and expansion of the other, and (3) utilization of the resources of the accepting person for help in those situations where help is needed and for protection against noxious forces. In most humans the desire to be acceptable to all others can be demonstrated, even though the desire to be accepted by people especially meaningful to them may be greater than the desire to be accepted by those of less significance in their lives.

In all, the need to be acceptable to at least one other person can be shown. Acceptance by others is necessary for survival, since, to varying degrees, it guarantees the availability of the resources of others or of the society as a whole to the individual. Ostracism from a tightly knit, homogeneous society has frequently been equivalent to a death sentence for the excluded person. Techniques for guaranteeing acceptance by others are developed from early life, and the earliest techniques are developed in relation to parents or their surrogates. The techniques and the value systems associated with them are conditioned by the approving, affectionate, and rewarding responses, or their opposite, of parents and surrogates. Important concepts concerning acceptable behavior are derived from cultural patterns and values. These are interpreted for and transmitted to the individual by his family and community. Certain concepts of acceptability, however, may be highly individual, reflecting the idiosyncratic aspects of pathological personality organization.

The need for acceptance by others, though constantly present, fluctuates quantitatively in a dynamic relationship with the strength of the feeling of need for others at any particular moment in a person's life history. The greater the need for others at any moment, the greater will be the need for acceptance and the more active and/or varied the techniques for acceptability. Helplessness in coping with the reality threat of a potentially fatal disease, such as cancer, places the person in a position where increased dependence on others is realistically necessary. Situations or states connected with increased needs for dependency on others increase the needs for acceptability. This promotes the exaggerated use of usual techniques, such as excessive cleanliness and conformity, the reinstatement of earlier techniques presumably renounced in the process of development (frequently called regressions), or the invention of new ones. In these situations the dependent attitudes are especially oriented to those persons perceived as powerful enough to cope with the specific threats and their resulting anxieties. Our observations indicate that these persons are generally the physicians and surgeons concerned with treatment. Devaluated self-esteem, associated with irrational concepts of personal culpability, i. e., sinfulness and badness, in the causation of their disease increases the feelings of unacceptability. Unfortunately, the feelings of unworthiness may lead the patient to doubt his acceptability to medical personnel and, according to the findings of Abrams and Finesinger, to misinterpret aspects of their behavior as evidence of rejection.

Confusion about dependency concepts exists in the psychiatric literature because of a failure to distinguish (1) normal dependent needs expressed in interdependent interaction with others, (2) heightened dependent needs mobilized by a crisis situation

or threat, and (3) a pathological adaptation in which control or possession of another's resources is believed to be the primary way of achieving personally significant goals and preventing the occurrence of injury or disease. Although it is not the purpose of this paper to provide this much-needed clarification, our experience indicates that in situations of crisis it is difficult to differentiate a chronically pathological dependent adaptation from heightened dependent needs arising from reality helplessness without careful investigation of the past history.

There is a group of people who, because the parental or cultural demands for acceptance were such as to preclude normal development or fulfillment of individual needs and experience, became pathologically independent characters. Mistrust of others, especially when help may be needed of others, is characteristic of this group. In the face of a reality situation demanding the help of others, members of this group fail to seek help or, in seeking it, face profound anxiety with paranoid decompensatory reactions.

As we have already indicated, situations of helplessness precipitated by the pressure of serious disease often promote an exaggerated need for acceptance and an increased fear of and sensitivity to rejection, with a consequent caricaturing of usual techniques of acceptability. In the patients we have observed, the techniques prominently involved were cleanliness, goodness, devotion to duty, industriousness and achievement, self-sacrifice, and submissiveness. When, in face of the increased helplessness and the increased need for acceptability, either the disease itself or the attendant necessary surgery produces a situation which precludes the use of one or more important techniques for acceptability, catastrophic threats to personality organization and functioning results. Patients with abdominoperineal resections for rectal carcinoma, in whom cleanliness was an important prerequisite for acceptability preoperatively, clearly demonstrate such mechanisms in their grossly excessive irrigation, massive withdrawal from social participation, and multiple compulsive practices.[6] The following formulations and case material further illustrate the dynamics of such mechanisms.

I. Reactions to the disruption of techniques of acceptability

A. The disruption of techniques of acceptability usually results in self-hatred and depression.

1. A mastectomy or hysterectomy may result in thinking, "I am ugly and unattractive, particularly to men."

"I feel terrible just even looking at that cut. There's nothing left in life for me. I was a woman and felt like any other woman. We're all born for love and affection. I wasn't any different. I wanted the same thing that other women wanted. How can I look at the scar on my body? I feel so disgusted when I look at the scar that I walk around without a shower for so long that potatoes are growing out of my feet. This cut disgusts me so much that I am afraid even to look at it. I curse myself. I used to think my body was beautiful. I would never go near a man now. I am frightened and would think that I did something bad. When a girl walks on the street she dresses to attract men. That's the way the whole life is. You want to look nice, but now I don't care. All of my ambition is gone with this operation."

2. A colostomy may result in thinking, "I'm dirty and smelly now and not fit for human companionship."

"My whole personality has changed since this happened to me. I got to be a sourpuss and am not the same person. I can't smile and be with people when I'm afraid that I'm oozing. The other night I felt this way and when I got home I was unclean. I'm afraid to be with people because I feel I might be dirty and smell. All I want is to be free to go among people and not imagine that they're sniffing and smelling me. I don't want to go to a hospital again even if I need to. I just don't like to be handled or touched because I am dirty and filthy and they have to wash and clean you. Whenever I spilled in the house I would have dreams that I was among people and it was coming out of me and they were running away from me."

Techniques for Preserving Health and Integrity

(or Controlling the Occurrence of Disease and Injury)

Identifiable in many of our patients were beliefs that by fulfilling their criteria for acceptability they were simultaneously guaranteeing themselves against the occurrence of either serious illness or injury. The dynamics of such beliefs contained the premise that powerful people or their supernatural extensions would protect them from harm if they were good. One corollary of these beliefs is that illness results from antisocial acts or transgressions against the wishes of authoritative figures. Such a concept of the causation of cancer was also verbalized by a number of patients in studies reported by Abrams and Finesinger[1] and Bard and Dyk.[3] These patients attributed their illness to occurrences such as contracting venereal disease and a variety of misdeeds, real or imagined. Another set of techniques for preserving health derives essentially from parental indoctrination and reflects parental and cultural convictions about health and disease. These techniques include such ideas as getting proper nourishment or enough sleep, keeping the bowels regulated, avoiding overindulgences, etc. Violation of these health codes was seen as the cause or a contributory factor by many patients.

When a serious illness like cancer occurs, previous beliefs about maintenance of health and integrity are profoundly challenged. The challenge to such basic conceptions provokes the appearance of anxiety reactions and depressive and paranoid responses. The pattern of the reaction is in large part determined by whether the original beliefs are maintained, significantly altered, or renounced. The retention of the original beliefs, in the face of so profound a reality threat as cancer and the attendant surgery usually necessary, requires the utilization of a variety of psychological defenses.

I. Reactions in which the original beliefs are maintained; i. e., "If I am good, nothing harmful will happen to me."

A. "I brought this on myself."

1. "I was bad and deserve punishment."

   This belief results in feelings of unworthiness and depression.

   "I believed God was punishing me for something I did wrong. We were always taught that if God sends you something it's for something you have done. I didn't question what sins I may have committed. I just felt I had to take it; it was my cross to bear. I could always take punishment when I deserved it. If we're punished, we're punished and that's all there is to it. When I deserved it, I knew I was bad."

2. "I didn't take care of myself."

   This belief results in self-condemnation, feelings of unworthiness, and depression, since its corollary is, "I could have prevented this from happening if only I had been more careful."

   "In my own family we were not rich but they cared for the children, and the children were well fed, had good food, good milk, fresh, clean vegetables. We had bread, not riches, but we were healthy. I only bought the best of food for my children, which was one of the first things I spent money for. Only one of my children had a serious sickness. The good food they had prevented other sicknesses. I could never understand how I got sick. I always ate good food. You know Jewish people only eat the finest and cleanest foods; so how could it come to me? I was ashamed because maybe my getting sick meant that I didn't eat good food."

3. "I did this to myself" is transformed into the belief, "He did this to me." The original depressive reaction, in turn, is changed to a paranoid one, or the two reactions fluctuate if the first belief is not banished.

   "Everybody makes her own bed and then has to lay in it. I say to myself, 'Why didn't I plan a different life for myself instead of going for an operation?' If I was fool enough to go

under this operation, I should have died under the knife. They frighten women and tell them that tumors will turn into cancers. I'd never get cancer even if I had 500 tumors. They put the fear of cancer into people's minds, and even if they are not sick to begin with, they get sick by worrying and thinking they get cancer after the doctor tells them that they have tumors. They develop cancer from fright."

B. "I have been good, but the world has been neglectful or unjust."

1. This belief preserves a sense of worth by blaming others. It results in depression with paranoid features, however, because of the failure of the technique of goodness to guarantee safety.

"I never squawked about anything and was always a good person. I never asked for anything or bothered anyone. I didn't want to burden anyone with my problems. I did everything for myself and was so clean. I'm sorry that I had the operation, and why didn't I call my sister, because she would have taken me out of the hospital. Instead I called on the wrong people for help. I called on my brother Jack, who says that he told me lots of things. I told him and his wife recently that I didn't want them to go to my funeral because they didn't stop me from going under the knife. They should have broken my feet to prevent me from going."

C. The transformation of a catastrophe into a privilege. "God chastises those whom He loves best." This belief is sometimes accompanied by feelings of exaltation and mania, constituting a manic equivalent. Even in the absence of exaltation, self-esteem is heightened because of thinking that the injury is a sign of special status and value.

"Sometimes I and my husband ask each other what we did to be punished so in having our son get leukemia. I don't feel that we have done anything wrong but, instead, have been good to our families and others. One of my friends said, 'God chooses his favorites to make them suffer,' and I feel that this may be right. In any case, God gave me my son to begin with, and I can do nothing if He wants to take him back."

II. Reactions in which the original beliefs are altered or renounced. The renunciation of beliefs may result in thinking, "I have no way of controlling illness now; I'm vulnerable." This, in turn, results in an inhibitory depression with anxiety.

"I did a lot of charitable work and when my cousin said it was God's will that people got sick I said it was nonsense and shouldn't happen to good people. Why don't people who cause war and destruction get sick and have operations like me? Why did it have to happen to me? I never did anyone any harm and was so good to everybody. My husband was in the fruit business and sent food anywhere I felt it was badly needed. I no longer believe in God if He would do that to me when I have been so good. People who murder and kill and do awful things to others are well, and I have done no harm to anyone."

III. Reactions in which current reality is altered or rejected to avoid any challenge to the original beliefs.

A. The mechanism of denial sustained by a paranoid reaction. "I had no disease. They just butchered me for their own advantage." This type of thinking results in depression over an undeserved fate and paranoid rage directed at the designated injurer.

"I was a healthy and strong girl. I could have lived to 500 years if people lived to 500 years. I was so strong until I came to this hospital that I would have lived not to 100, but at least to 150. Now all I ask for is a quick death, and I have never wanted to die. A lot of doctors don't know what they're doing. They just like to practice on you. I just hate doctors. I can't explain to you what butchers they are. They ruined my life. I had everything to live for before this operation."

Techniques of Mastery and Concepts of Bodily Integrity

In the last analysis, no technique of mastery or concept of one's physical integrity can be divorced from the larger context of relatedness to other people. Nevertheless, a group of depressive and paranoid responses can be related to beliefs such as "I have lost functions so important to my living that life is no longer worth while"; "I have been so mutilated that what is structurally left of me is not adequate for human living," and "I have not been made inferior by what has happened to me but am better than I was before."

A. The disruption of or interference with techniques of mastery.

1. A hysterectomy can result in believing that total functioning has been compromised, that the keystone organ has been removed.

"I used to feel so much better with it. A woman feels so much better when she menstruates. The mind works so much better with it. Everything feels so much different. Before, I felt like a little girl, and now I feel like an old lady. When a girl has her period she feels that if something goes wrong today, that tomorrow will be a good day. I swear that with my period I felt so much cooler and my brain worked so much better. They took away a woman's period, the most beautiful thing in life. You don't realize how important it is until you lose it."

2. The amputation of a limb can result in thinking that the limitation of motility eliminates or reduces the possibility of gratification or enjoyment in life from previously valued activities.

"I was a pretty active guy in work and sports. As much as a guy can cram into 35 years of enjoyment, I did. I had a full life, Doc. I did everything I wanted to. Everything I did I enjoyed—every bit of it. My only regret is that I can't do everything I did before; work, and play, everything. I feel that I've had it and will never be able to do what I enjoy, that is to the full extent of enjoying it. I have never dreamt of being a double amputee. All of my dreams have been just as if my life before I got sick was continuing without change. I work in the shop doing my ordinary duties, walking around and talking. I have spent several weekends fishing and hunting as I used to. The thing that's killing me, Doc, is hanging around the house. An old man couldn't stand that, and I'm only 41 years old. I would rather live only two years, if I could go out in any kind of weather and be on the move, than to hang around the house for ten years. What am I going to do, watch TV and see other people do what I used to do? That I can't take at all."

3. A loss of potency associated with urinary-tract difficulties and the disruption of confidence and adequacy associated with invalidism following abdominoperineal resection can result in the initial thought, "I am no longer a man and life is over," which is then transformed into "I am superior to other men."

"The fact is that after the operation I didn't care to live. Particularly when I knew I was, what do you call the word, impotent. After the operation it was impossible to come any more with my wife because there was no erection, and if there would occur such a thing then the complete seed has disappeared. It wasn't a good feeling. Life was insignificant to me for a long, long time. I don't know why this operation should be connected with that. Another man who has the same operation told me that he is still able to have intercourse with his wife, which made me feel worse. Before my operation I was a designer on ladies' knit goods. My branch was to make the patterns and to get out the styles. You could call it being a designer on ladies' dresses and suits. I took charge in a plant of about 20 to 25 people. After this, and until the operation, I was in a little business of my own. I made up samples and submitted them to job-

bers. If the jobber liked them, he would give an order for 100 dresses and those he rejected, he rejected. After the operation I didn't work for three or four years. I didn't have any confidence. I sold a new car and didn't think I would be able to come back at all. During this time I took in work at home and did it for artists. They gave me a picture, and I made them a suit of clothes; and since I'm a good craftsman, they were glad to make the exchange. One time Dr. B. examined me and said, 'Why don't you go back to work?' And since he said that he put a new thing in my life; he gave me courage. I didn't go back as a designer but as an operator on ladies' clothes because sitting was easier than walking around all day long.

Since the operation something else developed, Doctor. I think I have a kind of persecution complex—is that what they call it? Since after the operation the development comes, and it goes on. I feel that I'm disliked in my shop. I'm disliked among people. Either they feel that I'm superior to them, or they feel that I can work better than they do. In my own case maybe I'm a little bit too proud of myself. My foreman hates me, and I wouldn't like to leave because in the other place it might be the same development."

B. Reactions to the violations of body integrity by surgery. "My integrity has been so badly violated that what is left of me is not worth while living with." This belief results in profound depression and, in addition to involving feelings of inacceptability to others, focuses upon a tragic sense of incompleteness.

"Why did I go and have this done? Two-thirds of your body they took away. I don't even think they had to do it. Look what they did. It didn't bother me. My sister said, 'You wore falsies before; why worry now?' But it isn't that. I should thank God I'm living. To go through such an operation is no little thing. I feel self-conscious of it. Not only for men; it's for women too. I feel that way. When a woman puts on a dress, it's the most important part of her. I'm even ashamed to go home. The relatives come to see me, but in the neighborhood I feel worse. That's why I stayed away so long. I feel that everyone is looking at me. My whole system is different than before. My whole face is even changed. I even have blotches all over my face. Before I always used to be smiling; and it's terrible to be around a person who cries and broods, and I know it. They tell me you better get out of it, but I can't help it."

Comment

A thesis is proposed and supported by illustrative clinical observations that malignant disease and its treatment by radical surgery are a fundamental threat to many patients, not only because of the reality danger to survival and bodily integrity but also because of their impact upon adaptational patterns. The threat associated with malignant disease and surgery disrupts important adaptive techniques and profoundly challenges the beliefs and assumptions underlying these techniques. With the disruption of adaptive techniques, whose objective was the prevention of illness or injury, or the promotion of acceptability and self-respect, a crisis situation is created. The thinking associated with these techniques must be either affirmed or renounced; the significance of the event altered or its reality denied. Ordinarily the validity of these beliefs and assumptions is not subjected to critical testing except under special circumstances of life, such as serious disease. At such times evidence that might contradict their validity may be considered. Affirmations, renunciations, alterations of significance, and denial of reality are often accompanied by intense, overt affective reactions of depression, rage, and elation. In the following outline there have been summarized, under the headings of (1) depression, (2) paranoid reactions, and (3) elation, the nature of the adaptive techniques disrupted, the thinking processes basic to the affective reactions, and, wherever appli-

cable, whether the conviction underlying the techniques has been affirmed or renounced.

I. Depression
- A. Related to techniques for control of illness and injury
  - 1. "I brought this on myself."
    - (*a*) "I was bad and deserve punishment." — Technique preserved
    - (*b*) "I didn't take care of myself properly." — Technique preserved
  - 2. "I have been good, but the world has been neglectful and unjust." — Technique preserved
  - 3. "I have no way of controlling illness. I am vulnerable." (Inhibitory depression with anxiety) — Technique renounced
- B. Related to disruption of the techniques of mastery and techniques for maintaining acceptability consequent to disease and radical surgery
  - 1. Disruption of techniques of mastery
    - (*a*) Loss of limb: "I can't walk, dance, or participate in athletics, etc."
    - (*b*) Hysterectomy: "I can't have a baby," or the irrational belief, "I can no longer participate fully in sexual intercourse."
  - 2. Disruption of techniques of acceptability
    - (*a*) Colostomy: "I am dirty, smelly and no longer fit for human companionship."
    - (*b*) Mastectomy or hysterectomy: "I am ugly and unattractive, particularly to men."
- C. Related to violation of bodily integrity
  - 1. "What is left of me is not worth living with."
  - 2. "The functioning of my body has been compromised because important aspects of its structure have been destroyed."

II. Paranoid reactions
- A. Related to techniques for control of illness and injury
  - 1. "I haven't been bad. It's not my fault. Someone else did this to me." — Technique preserved
  - 2. Idea of neglect and poor care — Technique preserved
    - (*a*) "The world has neglected me and hasn't recognized my worth and goodness."
- B. Distortion of the fact of illness
  - 1. Derivative of the mechanism of denial
    - (*a*) "I am not sick. The surgeon operated on me to experiment."
  - 2. Derivative of the mechanism of denial and attribution of illness to the malevolence of another person
    - (*a*) "The surgeon made me sick so he could practice on me."
- C. Interference with techniques of mastery
  - 1. Despair is transformed into a belief about one's superiority to others, accompanied by irrational expectations of injury
    - (*a*) "I am no longer a man," is changed to "I am superior to other men who resent me because of this."

III. Elation
- A. The significance of illness is altered
  - 1. A catastrophe is transformed into a privilege
    - (*a*) "God chooses his favorites to make them suffer."

One of the important observations which emerge from inspection of this outline is that the assignment of blame is a critical factor in both depressive and paranoid reactions related to the disruption of techniques for maintaining control over illness and injury. The decision-making process in assigning the direction of blame determines which of the two reactions results. Where blame is attributed to the self, feelings of unworthiness and badness are prominent; guilt is experienced, and depression occurs. Where blame is assigned to others, feelings of worthiness and goodness are prominent; anger is experienced over unjustified injury, and paranoid reactions occur. The factors determining assignment of blame are complex and beyond the scope of this study. The paranoid reaction, however, whether it is intended to or not, protects the patient against the depressive reaction resulting from self-blame. The occurrence of self-referred guilt frequently is associated with an attempt to preserve techniques of control over illness and injury. In effect, what is implied is the assumption that what has occurred is due not to the invalidity of the beliefs and adaptive techniques but, rather, to the patient's failure to follow them. Guilt in this context has two important functions. The first is to preserve interpersonal relations through the declaration, "I have been bad; I want to repent and be forgiven." The relationship may be with actual or

symbolized figures of authority or with their supernatural extensions. The second function of guilt, as already indicated, is to preserve the techniques utilized for illusory control over illness and injury, and the associated beliefs, which constitute an important conception of reality.

Schmideberg,[7] in a discussion which also points out the multiple functions that can be served by guilt, emphasizes that under certain circumstances the assumption of responsibility is preferable to a sense of helplessness.

> Guilt implies responsibility; and however painful guilt is, it may be preferable to helplessness. Medieval man believed that the plague was a punishment for his sins; by castigating himself, he hoped to atone to God and for every evil. He had no other alternative in his helplessness.

What is implied in this formulation, as well as in our own, is that the irrational assumption of personal responsibility goes hand in hand with an insistence upon omnipotent control, which is preferred to the acceptance of actual helplessness in certain situations. This leads to an unrealistic conception of personal responsibility where responsibility does not exist and control is not possible. With atonement or expiation for past misdeeds which are attributed a causative role in disease, and a resolution to be good or righteous in the future, the sense of helplessness is dissipated and an illusory control over illness and injury regained.

The assignment of blame following the occurrence of injury or illness, irrespective of the direction of the blame, presupposes the assumption that control is still possible. In self-blame the implication is: "I failed to do what is effective or to behave in such a way that I could induce others to prevent the occurrence of injury and illness." The belief which accompanies the assignment of blame to others or judgment of failure on their part is one of being entitled to what has not been accomplished in one's behalf or of others intentionally producing the harm for their own selfish purposes. When the injury is attributed to another's malevolence or exploitativeness, there is frequently a history of perceiving significant people in the environment prior to the current experience as hostile and/or manipulative.

Sullivan[8] has also emphasized the importance of blaming others in the development of paranoid reactions. He has formulated, moreover, that "the essence of the paranoid dynamism is the transference of blame" (page 147), a formulation with which we are not in agreement, since in our data the development of paranoid reactions has been observed also in relation to irrational expectations of injury where blame played no role. An important contribution to an understanding of the processes involved in paranoia was made, however, by his pointing out that transference of blame, when it does occur, is protected against challenge or critical testing by others through the invention of a rationale for the imputed hostility or persecution. For patients with malignant disease the rationale for explanation of injury by others, e. g., producing cancer or performing unnecessary surgery, is frequently (1) the need for practice in order to improve surgical skill, or (2) pecuniary gain.

The mechanism of denial is implicitly basic to both depressive and paranoid reactions which occur in response to the disruption of magical techniques for the control of illness and injury. What is denied is the fact that such omnipotent control is impossible or that a state of helplessness exists in the face of a grave threat to survival. In certain of the paranoid reactions this reaches the point where any knowledge about the occurrence of the disease or its seriousness is denied and the disease and its treatment are attributed to the malevolence of another person. This maneuver is a form of indirect insistence upon the possibility of control over disease and injury. The person to whom the malevolent causation of disease or its unnecessary treatment is attributed is irrationally delegated the power to bring about a dread illness or to flout professional ethics and community morals without fear of retaliation.

Some of the reactions involving either self-blame or blame of others are not necessarily irrational. There are situations in which patients, because of their fears of learning about threatening realities, have caused unnecessary delay in diagnosis and treatment. In view of the widely disseminated information about the necessity for early diagnosis and prompt treatment, patients who blame themselves for unnecessary delay in diagnosis and treatment have some reality basis for their depression. Similarly, patients who have not benefited from advanced medical knowledge because of professional deficiencies in care have some reason for resentment and blame.

Where disease and its treatment have either limited or destroyed continued participation in activities which are prized sources of gratification, the ensuing psychologic reactions, such as depression, are not necessarily evidence of psychopathology. For instance, in the case of an athlete or a dancer who has had a leg amputation for a sarcoma, a reality adaptation has been disrupted by the curtailment of motility. The crisis provoked does not require the reconciliation of illusion and reality, but, instead, necessitates adapting to the loss of prized sources of gratification and fulfillment. The task which has to be accomplished, therefore, is the utilization of alternative techniques for the attainment of the same objectives or a reorientation in which substitute sources of gratification acquire value. Neither will be attempted if the patient does not believe that the objectives are possible of attainment or if he is committed to the conviction that what has been lost is primarily what made life worth while for him.

Summary

The concepts which have been discussed were derived from the study of a group of nonpsychiatric patients at a time of dramatic crisis in their lives when they were faced with a potentially fatal disease and mutilative surgery. We observed the elaboration of a group of depressive and paranoid reactions, extensive denials, and, less frequently, elation which were related to the disruption of (1) techniques of acceptability, (2) techniques of mastery, and (3) techniques of magical control over disease and injury, and the violation of concepts of bodily integrity. We do not mean to propose that all depressive and paranoid reactions are related to such mechanisms, but we do believe that the application of these principles in a psychiatric population would also increase current understanding in that group.

444 East 68th St. (21).

REFERENCES

1. Abrams, R., and Finesinger, J.: Guilt Reactions in Patients with Cancer, Cancer 6:474-482, 1953.

2. Bard, M.: Use of Dependence for Predicting Psychogenic Invalidism Following Radical Mastectomy, J. Nerv. & Ment. Dis. 122:152-160, 1955.

3. Bard, M., and Dyk, R. B.: Psychodynamic Significance of Beliefs Regarding the Cause of Serious Illness, Psychoanalyt. Rev. 43:146-162, 1956.

4. Cantril, H., and others: Psychology and Scientific Research, in Human Behavior from the Transactional Point of View, edited by F. P. Kilpatrick, Hanover, N. H., Institute for Associated Research, 1952, pp. 195-212.

5. Drellich, M. G.; Bieber, I., and Sutherland, A. M.: Psychological Impact of Cancer and Cancer Surgery: VI. Adaptation to Hysterectomy, Cancer 9:1120-1126, 1956.

6. Orbach, C. E.; Bard, M., and Sutherland, A. M.: Fears and Defensive Adaptations to the Loss of Anal Sphincter Control, Psychoanalyt. Rev., to be published.

7. Schmideberg, M.: Multiple Origins and Functions of Guilt, Psychiat. Quart. 30:471-477, 1956.

8. Sullivan, H. S.: Clinical Studies in Psychiatry, edited by H. S. Perry, M. L. Gawel, and M. Gibbon, New York, W. W. Norton & Company, Inc., 1956.

9. Sutherland, A. M.; Orbach, C. E.; Dyk, R. B., and Bard, M.: Psychological Impact of Cancer and Cancer Surgery: I. Adaptation to the Dry Colostomy, Cancer 5:857-872, 1952.

Adrenocortical Response and Phosphate Excretion in Schizophrenia

Comparison of Catatonic and Paranoid Schizophrenic Men and Normal Men

J. A. F. STEVENSON, M.D.; J. B. DERRICK, Ph.D.; G. E. HOBBS, M.D., and E. V. METCALFE, M.D., London, Ont., Canada

There is increasing evidence that the autonomic nervous system and the endocrine system function abnormally in several psychiatric disorders. This abnormal function may, or may not, be of causal importance in these diseases; nevertheless, its definition will contribute to an understanding of these diseases. Abnormalities of adrenocortical function in schizophrenia have been suggested by the studies of Hoagland and his colleagues [1,2] and by those of others.[3-5] Some studies [6,7] have, however, not supported this suggestion.

In 1953 we also observed that in a group of schizophrenics the eosinophil responses to the standard corticotropin and epinephrine tests [8] were often less than normal. Particularly noticeable was a lower resting level of circulating eosinophils in the catatonic than in the paranoid schizophrenics. The fall in eosinophils following corticotropin was, however, greater in the former than in the latter. The eosinophil response to corticotropin is considered an approximate index of adrenocortical function,[9] and it was, therefore, decided to examine the possibility of a difference in adrenocortical function between the catatonic and paranoid subgroups of schizophrenia by more specific measurements of the function of this gland.

Submitted for publication Jan. 31, 1957.

This study was supported by a grant from the Department of Veterans Affairs (Canada).

Preliminary communications of these results were made to the Canadian Physiological Society on Oct. 22, 1954, and Oct. 19, 1956.

From the Department of Psychiatry and the Clinical Investigation Unit, Westminster Hospital (D. V. A.), and the Departments of Physiology and Psychiatry, University of Western Ontario, Faculty of Medicine.

Procedure

For this investigation the psychiatric service was asked to provide 20 catatonic and 20 paranoid schizophrenic patients who were in a chronic state, yet not deteriorated beyond cooperation in the tests. The diagnosis of the individual patient was unknown to the experimental team until all the results had been compiled. For various reasons, the number of patients in each group providing complete results was 18 catatonics and 21 paranoids. Twenty healthy hospital orderlies who, in general, lived in the same physical and nutritional environment as the patients agreed to serve as controls. The mean (±S. D.) age and duration of stay in hospital for each of the three groups of subjects were as follows:

	No.	Age, Yr.	Stay in Hospital, Mo.
Normal	20	35±7.2	..
Catatonic	18	37±3.6	74±40.1
Paranoid	21	39±7.2	58±34.4

All subjects submitted to three different experimental days, which, for each subject, were separated by at least a week. Table 1 shows the precise schedule on these days. On the experimental days the subjects went without food until the test had been completed. This procedure is similar to that used by Hoagland et al.[1] The schizophrenic patients had each been exposed to a sham control day to accustom them to the procedure and lessen any anxiety.

The urine was collected for the three periods, the bladder being emptied at the beginning and end of each period. The latter sample was included in the collection for that period. The following measurements were made on each urine sample: volume, creatinine, uric acid according to Benedict and Franke, and inorganic phosphate according to Fiske and Subbarow, as described by Hawk, Oser, and Summerson [10]; sodium and potassium, using the lithium internal-standard

TABLE 1.—*Experimental Schedule*

Period		Day I Control	Day II Corticotropin *	Day III Epinephrine †
1:	7:00-9:00 a.m.	I-1 Control	II-1 Control	III-1 Control
	9:00 a.m.	--	Corticotropin 25 mg. i.m.	Epinephrine 0.3 mg. s.c.
2:	9:00-10:15 a.m.	I-2	II-2	III-2
3:	10:15 a.m.-12:15 p.m.	I-3	II-3	III-3

* Adrenocortphic hormone Connaught Medical Research Laboratories, University of Toronto, Toronto, Ont.; Lot No. 29-1.
† Adrenalin chloride (epinephrine hydrochloride) Parke, Davis & Company, solution 1:1000.

method with a Perkin-Elmer flame photometer, and 17-ketosteroids, extracted according to Robbie and Gibson[11] and determined colorimetrically by the method of Callow, Callow, and Emmens.[12]

Samples of finger prick blood were taken at 9:00 and 10:15 a.m. and at 12:15 p.m., for eosinophil counts.[13] In the last half of each group a sample of venous blood was taken at 12:15 p.m. for determination of serum inorganic phosphate by the method of King.[14]

The results were treated by standard statistical methods.[15]

Results

The mean excretion rates of the normal controls, the combined schizophrenic group, and the catatonic and paranoid subgroups during the control period on Days I, II, and III are shown in Table 2; the means of the control period on each of the three days were remarkably constant in any one group.

To obviate, to some extent, the influence of possible group differences in diurnal variation,[16] the average rates for the whole five-hour period (7:00 a.m.-12:15 p.m.) on the control day are compared in Table 3.

Since the major interest was the comparative response to stimulation of the adrenocortical system in these subjects, the results for the periods after stimulation have been stated as the percentage change from the prestimulation rate. This was calculated for each subject, for each index and period. Figures 1A, 1B, and 1C record the means of these observations for the various groups.

There was no difference in the urine flow of the various groups during Period I. As the morning passed, the urine flow increased markedly except after the administration of corticotropin, when it was reduced, probably a reflection of the increased retention of sodium. Polyuria has been observed in schizophrenia[7]; in the present study this

TABLE 2.—*Average Rate of Output in Control Periods of Three Experimental Days*

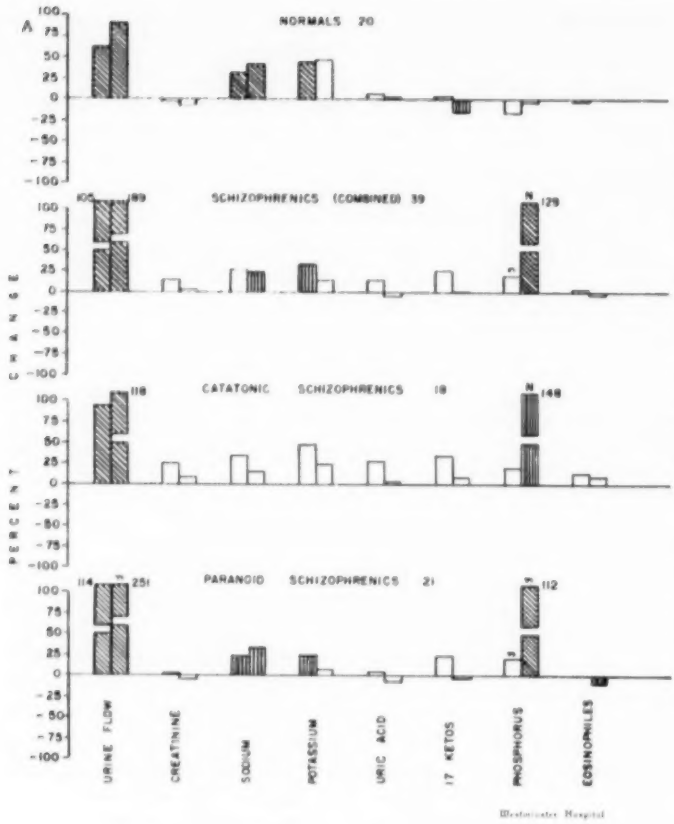
	Period I: Days I, II, III							
Group *	Urine Vol., Ml/Min.	Creatinine, Gm/24 Hr.	Sodium, Mg/Hr. †	Potassium, Mg/Hr.	Uric Acid, Mg/Min.	17-Ketosteroids, Mg/Hr. †	Phosphorus, Mg/Min.†	Eosinophils, Count/Cu. Mm.
N	1.2±0.14 ‡	1.71±0.066	161±10.6	149±12.8	0.46±0.028	0.64±0.040	0.41±0.032	167±36.4
S	1.1±0.09	1.66±0.057	208±10.6 n	155±10.3	0.43±0.017	0.80±0.046	0.29±0.021 n	165±19.1
CS	1.0±0.11	1.57±0.087	213±17.3 n	146±17.6	0.42±0.028	0.82±0.071 n	0.23±0.014 n	127±20.8
PS	1.3±0.13	1.74±0.073	204±13.3 n	162±11.9	0.43±0.017	0.78±0.059	0.34±0.032 c	197±29.3

* N=normals (20); S, combined schizophrenics (39); CS, catatonic schizophrenics (18); PS, paranoid schizophrenics (21).
† Superscripts N, S, C(S), P(S) indicate significant difference ($P<0.01$) from group named; n, s, c(s), p(s) indicate probable significant difference ($P<0.05$) from group named.
‡ Mean±S.E.M.

TABLE 3.—*Average Rate of Output in All Three Periods of the Control Morning*

	7:00 A.M.—12:15 P.M.							
Group *	Urine Vol., Ml/Min.	Creatinine, Gm/24 Hr.	Sodium, Mg/Hr. †	Potassium, Mg/Hr.	Uric Acid, Mg/Min.	17-Ketosteroids, Mg/Hr. †	Phosphorus, Mg/Min. †	Eosinophils, Count/Cu. Mm.†
N	1.3±0.16 ‡	1.69	167±10.5	176	0.46	0.60±0.042	0.36±0.043	131±29.6
S	2.0±0.06 n	1.64	222±15.0 n	156	0.42	0.75±0.053 n	0.33±0.027	161±22.4
CS	1.7±0.23	1.56	226±21.0	152	0.40	0.76±0.074	0.26±0.031	118±23.2
PS	2.2±0.25	1.72	219±21.7	165	0.43	0.73±0.079	0.40±0.036 n	197±35.1 c

* N=normals (20); S, combined schizophrenics (39); CS, catatonic schizophrenics (18); PS, paranoid schizophrenics (21).
† Superscript C indicates significant difference ($P<0.01$) from group named; n and c, probable significant differences ($P<0.05$) from group named.
‡ Mean±S.E.M.



Figs. 1A-1C. — Comparison of responses of the normal, combined schizophrenic, and catatonic and paranoid schizophrenic groups on the control day (Fig. 1A) and to corticotropin (Fig. 1B) and epinephrine (Fig. 1C). The response is expressed as the percentage change from the control period (7:00-9:00 a. m.) during the first (9:00-10:15 a. m.) and second (10:15 a. m.-12:15 p. m.) periods after administration of the agent. Hatched bars indicate a significant change for the group from its control level (7:00-9:00 a. m.); diagonal, $P<0.01$; vertical, $P<0.05$. A letter above a bar indicates a significant difference in response from the group indicated by that letter; e. g., *N* indicates $P<0.01$; *n* indicates $P<0.05$ (Table 2, footnote).

characteristic was particularly noticeable in the paranoids.

The excretion of creatinine was almost the same in all groups and, as expected, remained fairly constant in the normals under all conditions. Corticotropin reduced it in the paranoid group, and epinephrine increased it in the schizophrenic group.

During Period 1, the schizophrenic group showed a significantly higher excretion of sodium than the normal group. All groups increased their rate of excretion during the last two periods on the control day, but the schizophrenics continued to remain above the normals during this control morning (Table 3). This high excretion of sodium, in the morning at least, has been noticed in schizophrenics by other investigators.[17,18] There was little difference between the normals and the schizophrenics in potassium excretion on the control day. Corticotropin depressed sodium excretion even more in the catatonics than in the normals or paranoids (Fig. 1B). On the other hand, the catatonics showed the least increase in potassium excretion after corticotropin. If anything, epinephrine inhibited the increase in both sodium and potassium excretion during the morning (Fig. 1C). Indeed, it caused a significant retention of potassium in the schizophrenics.

Figure 2 demonstrates the sodium-potassium excretion ratio for the several groups. The effect of corticotropin was typical in all groups. After epinephrine there was no change in the normals, but in both the catatonic and the paranoid schizophrenics the sodium-potassium ratio rose sharply. This

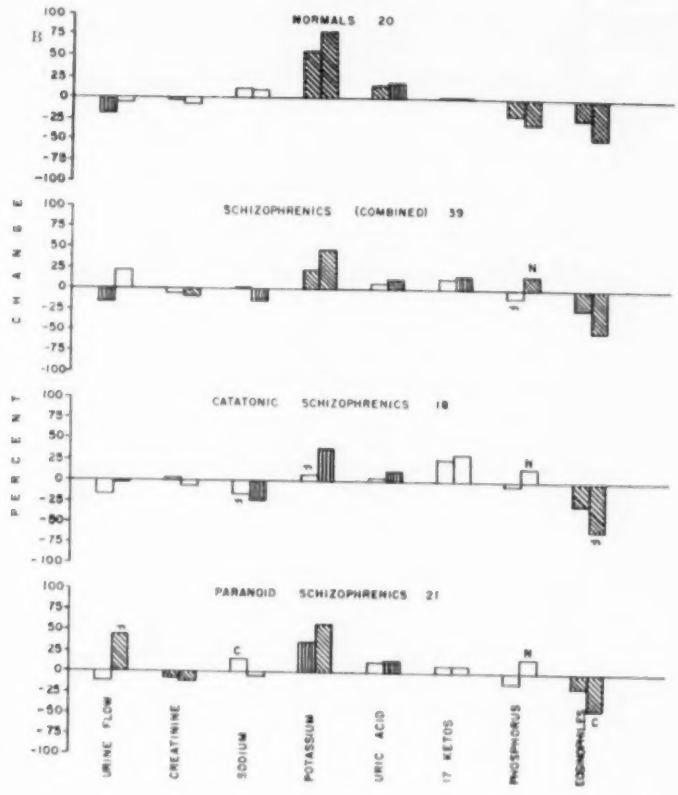


Figure 1B

increase was largely due to a marked reduction in the excretion of potassium (Fig. 1C).

All groups showed a similar level of uric acid excretion in Period 1, and this remained fairly constant throughout the control morning except in the catatonic group, which showed a wide variation. Corticotropin produced an increased secretion, significant in all groups, but epinephrine caused no significant changes.

The rate of 17-ketosteroid excretion was higher in the schizophrenic groups than in the normals during the control periods. This difference approaches significance for the schizophrenics as a whole, and, indeed, it is probably significant for the catatonic group alone. A relatively high output of 17-ketosteroids has been observed frequently [7] in schizophrenics.

Corticotropin had surprisingly little effect on the 17-ketosteroid excretion except in the catatonic group, which showed an increase of probable significance. Administration of epinephrine also caused little change except in the paranoids, and in these the individual variation was great.

The schizophrenics showed a markedly lower excretion of phosphate than the normals during the control periods, and, although both subgroups contributed to this low level, it was the catatonics who were outstanding, with an excretion which was significantly less even than that of the paranoids (Table 2). The rate of excretion in both schizophrenic groups rose markedly during the control morning, whereas that of the normals remained fairly constant (Fig. 1A). Despite this increase, the catatonics

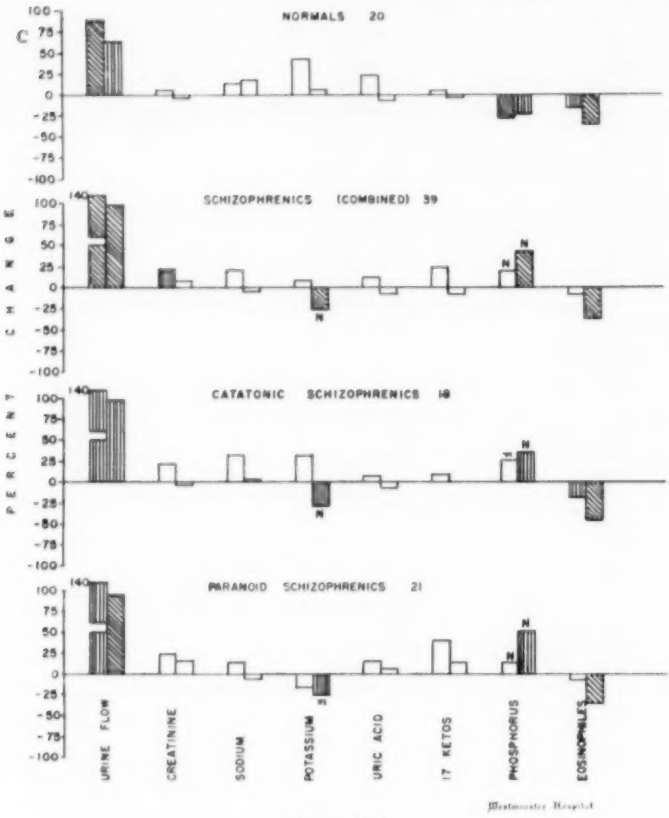


Figure 1C

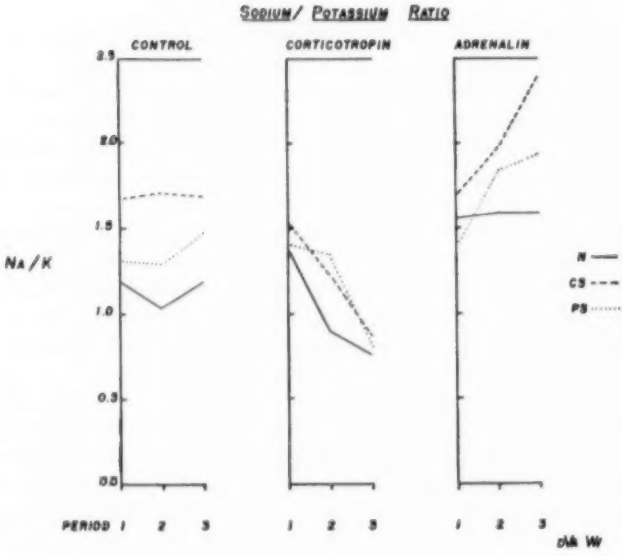


Fig. 2.—Changes in sodium-potassium excretion ratio shown by the normals (*N*), catatonic schizophrenics (*CS*), and paranoid schizophrenics (*PS*) on the control day and after corticotropin and epinephrine.

TABLE 4.—*Serum Phosphate Levels*

Group *	Day I Control†	Day II Corticotropin†	Day III Epinephrine
N	3.5±0.12‡	**2.9±0.13**§	3.7±0.07
S	3.9±0.13	3.6±0.19[s]	3.9±0.06
CS	4.2±0.16[n]	3.7±0.30[n]	4.0±0.13
PS	3.6±0.16[s]	3.4±0.22[n]	3.9±0.13

* N=normals (20); S, combined schizophrenics (39); CS, catatonic schizophrenics (18); PS, paranoid schizophrenics (21).
† Superscripts N, S, C(S) P(S) indicate significant difference ($P<0.01$) from group named; n, s, c(s), p(s) indicate probable significant difference ($P<0.05$) from group named.
‡ Mean (milligrams per 100 ml.) ± S.E.M.
§ Boldface indicates significant difference from control day ($P<0.01$).

excreted much less than either the paranoids or the normals throughout the control morning (Table 3). Corticotropin caused a significant fall in phosphate excretion by the normals in both Period 2 and Period 3, and in the schizophrenics prevented the marked rise seen at these times on the control day (Fig. 1B). Nevertheless, the schizophrenic group as a whole still showed a significant increase in Period 3 as compared with Period 1. The effect of epinephrine was very similar to that of corticotropin, a significant fall in the normals and a lessened increase in the schizophrenics, although the latter still excreted significantly more in Period 3 than in Period 1.

The serum phosphorus was included in the measurements made on the last half of each group. It was feasible to take only one sample of venous blood, and this was done at the end of Period 3 (12:15 p. m.). Table 4 shows the results. On the control day the level for the catatonics was significantly higher than that for either the normals or the paranoids. After corticotropin, the serum phosphorus was significantly lower in the normals, not only when compared with their own level on the control day but also when compared with the levels in the schizophrenic groups after corticotropin. All groups, however, did show a tendency to fall. Epinephrine appeared to have little effect on the serum phosphorus, although its effect on the urine phosphorus had been similar to, if less than, that of corticotropin.

Pincus, Hoagland, and associates [1,17,19] observed a lower excretion of phosphorus in their schizophrenics than in the normals during the 7:00-9:00 a. m. control periods. The present study suggests that it is the catatonics who are responsible for this difference (Table 2) and that they maintain this lower excretion throughout the morning (Table 3). The significantly higher serum phosphate found in the catatonics at the end of the control morning (Table 4) supports the conclusion that these patients had excreted less than the normals or paranoids throughout the morning.

The circulating level of eosinophils in the general schizophrenic group was similar to that in the normals at 9:00 a. m., but this similarity was due to an equidistant separation of the catatonic and paranoid groups above and below this level. Indeed, the difference between the low level in the catatonics and the high level in the paranoids approaches significance and is apparent

TABLE 5.—*Responses to Corticotropin and Epinephrine Corrected for Concurrent Spontaneous Changes*

Index	Group*	Day II Corticotropin Period 3	Day III Epinephrine Period 3
Urine volume	N	−95	−26
	S	−167	−91
	CS	−120	−19
	PS	−208	−155
Creatinine	N	+1	+6
	S	−12	+5
	CS	−14	−11
	PS	−8	+20
Sodium	N	−32	−24
	S	−30	−28
	CS	−37	−14
	PS	−40	−40
Potassium	N	+32	−41
	S	+32	−43
	CS	+16	−53
	PS	+48	−31
Uric acid	N	+17	− 8
	S	+16	−10
	CS	+13	−11
	PS	+22	+14
17-Ketosteroids	N	+16	+11
	S	+16	+ 5
	CS	+23	− 9
	PS	+11	+17
Phosphate	N	−27	−22
	S	−111	−85
	CS	−130	−113
	PS	−94	−60
Eosinophiles	N	−43	−33
	S	−48	−37
	CS	−67	−55
	PS	−32	−22

* N=normals; S, combined schizophrenics; CS, catatonic schizophrenics; PS, paranoid schizophrenics.

throughout the control morning (Table 3). All groups showed a significant response to corticotropin, but this was greater in the catatonics than in either the paranoids or the normals (Fig. 1B). Epinephrine also caused a significant fall in all groups; again, the catatonics tended to be the most responsive.

The difference between the catatonics and the paranoids in the resting level of eosinophils and the greater response to corticotropin in the former confirm our earlier observation of a difference in this index between these two subgroups of schizophrenia.[8]

If the control day truly indicates the spontaneous diurnal variation occurring during the experimental period, then subtraction of the relative changes on this day from those occurring after the administration of corticotropin and epinephrine may demonstrate more clearly the net or specific effect on these agents. Table 5 shows the results of such correction applied to Period 3. In most indices the differences in response between groups are much reduced. In fact, the "corrected" responses to corticotropin of sodium, potassium, uric acid, and 17-ketosteroid excretion are remarkably similar in all groups. The drop in eosinophils is also similar in the normal and schizophrenic groups, but there is still greater response in the catatonics than in the paranoids. Whereas corticotropin showed little net effect on creatinine excretion in the normals, it caused, if anything, an increased retention in the schizophrenics. Corticotropin now appears to have caused a marked reduction in urine flow in all groups, particularly in the paranoids. Most contradictory, however, is the "corrected" effect of corticotropin on phosphate excretion; rather than increasing it in the schizophrenic groups, corticotropin caused a reduction greater even than that in the normals. Despite this relative retention as compared with the control day, the serum phosphate at the end of the corticotropin day was lower in all groups, significantly so in the normals. This would imply that phosphate must have entered the cells, including bone, or must have been lost from the intestine as a result of the adrenocortical stimulation. This particular interpretation of our data does not agree with the supposition of Hoagland et al.[19] that in schizophrenia adrenocortical secretions facilitate the release of a phosphate bound in excess by the tissues. These workers did not, apparently, measure the spontaneous changes in phosphate excretion on a control morning and therefore assumed that corticotropin had caused the increase in phosphate excretion that they observed to follow in time the a. m.) our schizophrenics showed no differ- administration of this hormone.

Comment

During the control periods (7:00-9:00 ence from the normals in the rate of urinary excretion of water, creatinine, uric acid, or potassium, but a higher level of sodium and 17-ketosteroid excretion and a lower level of phosphate excretion. When the whole control morning (7:00 a. m.-12:15 p. m.) is considered, these differences are still apparent, and the tendency of the schizophrenics to polyuria also becomes apparent. When the schizophrenics are separated into catatonic and paranoid, it is seen that the increased excretion of water, sodium, and 17-ketosteroids at this time is common to the two groups, whereas the decreased excretion of phosphate is peculiar to the catatonics. The level of circulating eosinophils is lower in the catatonics and higher in the paranoids than in the normals.

The responses to corticotropin in our normal and schizophrenic subjects (Fig. 1B) were similar for most indices in direction, if not always in degree, to those observed by Hoagland et al.,[1,2] particularly in their older and longer-hospitalized group, although the increases in excretion of uric acid and of 17-ketosteroids in our normals were not as great. Among our schizophrenics, it was the catatonic group which showed a significant increase in 17-ketosteroids and the greater drops in urinary sodium and

circulating eosinophils following administration of corticotropin. This agrees with our earlier suggestion[8] in 1953 that the adrenocortical system is more reactive in catatonic than in paranoid schizophrenics. Although the increase in phosphate excretion following corticotropin was not as great in these schizophrenics as that observed by Hoagland et al.,[19] the difference from the normals is significant and in the same direction as that reported by them. There was no difference between the catatonic and paranoid subgroups in this response. When, however, the apparent effect of corticotropin on phosphate excretion is corrected for the spontaneous changes in this excretion on the control day, the net effect of stimulation of the adrenal cortex in the schizophrenics is shown to be a retention of phosphorus. Indeed, the "corrected" responses to corticotropin of sodium, potassium, uric acid, and 17-ketosteroid excretion are remarkably similar in all groups.

Compared with the normal, these schizophrenics had a higher renal excretion of water and salt, suggestive of a lower secretion of mineralocorticoid, but they also showed a higher excretion of 17-ketosteroids. The clinical distinction between catatonic and paranoid schizophrenia appears to be associated with metabolic differences; e. g., as compared with the paranoids, the catatonics showed a lower rate of urinary phosphate excretion despite a higher level of serum phosphate, a lower level of circulating eosinophils, and a greater fall in this level in response to corticotropin. These differences do not lead to a clear definition of hyper- or hypofunction of the adrenal cortex in either group, but they do demonstrate that these categories of schizophrenia vary as much from one another as either does from the normal group. When metabolic differences from the normal do exist, they are usually greater in the catatonic.

We are well aware of the importance of variations in the diurnal cycle of these indices[16] and of the fallibility of diagnostic categorization within the schizophrenic group. Investigation of the diurnal rhythm of phosphate excretion in these and other schizophrenic patients is now in progress.

Summary

The variations in several indices of adrenocortical activity have been measured in 20 hospital orderlies, 18 catatonic schizophrenics, and 21 paranoid schizophrenics throughout a control morning (7:00 a. m.-12:15 p. m.) and other mornings before and after the administration at 9:00 a. m. of corticotropin (25 mg. i. m.) or of epinephrine (0.3 mg. s. c.).

During the control periods the catatonics excreted less ($P<0.01$) phosphate than did the normals or the paranoids and more ($P<0.05$) 17-ketosteroids than the normals. Both schizophrenic groups excreted more ($P<0.05$) sodium than the normals; their urine volume also tended to be greater.

Both schizophrenic groups increased their excretion of phosphate as the morning progressed, but the normals maintained a relatively stable rate. After both corticotropin and epinephrine the excretion of phosphate was higher in the schizophrenics than in the normals, but when the spontaneous rate observed on the control day is subtracted from that observed after corticotropin the net effect of this agent appears to be a retention of phosphate.

As previously reported, the resting level of circulating eosinophils was lower and the response to corticotropin greater in the catatonics than in the normals or the paranoids.

These results support the suggestion that catatonic and paranoid schizophrenics differ as much from one another as they do from normals and suggest that the phosphate metabolism in this disease is worth intensive study.

Prof. R. J. Rossiter advised; Miss S. Paul, R.N., assisted in the clinical study, and Miss A. Hanley, Miss B. Herold, and Mrs. C. Sereny, aided in the laboratory aspects of the investigation.

346 South St.

REFERENCES

1. Hoagland, H.; Pincus, G.; Elmadjian, F.; Romanoff, L.; Freeman, H.; Hope, J.; Ballan, J.;

Berkeley, A., and Carlo, J.: Study of Adrenocortical Physiology in Normal and Schizophrenic Men, A. M. A. Arch. Neurol. & Psychiat. 69:470, 1953.

2. Hoagland, H.: Some Considerations of Adrenocortical Physiology in Relation to the Psychoses, Internat. Rec. Med. 166:183-189, 1953.

3. Hemphill, R. E., and Reiss, M.: Experimental Investigations in the Endocrinology of Schizophrenia, Proc. Roy. Soc. Med. 41:533-540, 1948.

4. Reiss, M.: Investigations into Psychoendocrinology, Internat. Rec. Med. 166:196-203, 1953.

5. Faurbye, A.; Vestergaard, P.; Kobbernagel, F., and Nielsen, A.: Adrenal Cortical Function in Chronic Schizophrenia (Stress, Adrenaline-Test, ACTH-Test), Acta endocrinol. 8:215-246, 1951.

6. Altschule, M. D.: Adrenal Function in Some Psychiatric Disorders, Internat. Rec. Med. 166: 190-195, 1953.

7. Altschule, M. D.: Bodily Physiology in Mental and Emotional Disorders, New York, Grune & Stratton, Inc., 1953.

8. Stevenson, J. A. F.; Metcalfe, E. V., and Hobbs, G. E.: Eosinophile Response in Schizophrenic Patients, A. M. A. Arch. Neurol. & Psychiat. 70:802-812, 1953.

9. Laidlaw, J. C., and Jenkins, D.: Stress and Eosinophils, J. Clin. Invest. 32:581, 1953.

10. Hawk, P. B.; Oser, B. L., and Summerson, B. L.: Practical Physiological Chemistry, Ed. 13, New York, The Blakiston Company, Inc. (Division of Doubleday & Company, Inc.), 1954.

11. Robbie, W. A., and Gibson, R. B.: Rapid Clinical Determination of Urinary 17-Ketosteroids, J. Clin. Endocrinol. 3:200, 1943.

12. Callow, N. H.; Callow, R. K., and Emmens, C. W.: Colorimetric Determination of Substances Containing the Grouping—CH_2CO—in Urine Extracts as an Indication of Androgen Content, Biochem. J. 32:1312, 1938.

13. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: Test for Adrenal Cortical Insufficiency: Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. 137: 1005, 1948; correction, p. 1544.

14. King, E. J.: The Colorimetric Determination of Phosphorus, Biochem. J. 26:292, 1932.

15. Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology, Ed. 4, Ames, Iowa, The Collegiate Press, Inc., 1946.

16. Hobbs, G. E.; Goddard, E. S., and Stevenson, J. A. F.: The Diurnal Cycle in Blood Eosinophils and Body Temperature, Canad. M. A. J. 70:533, 1954.

17. Pincus, G.; Hoagland, H.; Freeman, H.; Elmadjian, F., and Romanoff, L.: A Study of Pituitary-Adrenocortical Function in Normal and Psychotic Men, Psychosom. Med. 11:74, 1949.

18. Pincus, G., and Hoagland, H.: Adrenal Cortical Responses to Stress in Normal Men and in Those with Personality Disorders, Am. J. Psychiat. 106:641, 1949-50.

19. Hoagland, H.; Rinkel, M., and Hyde, R. W.: Adrenocortical Function and Urinary Phosphate Excretion, A. M. A. Arch. Neurol. & Psychiat. 73:100, 1955.

Effects of Lysergic Acid Diethylamide (LSD) on the Time Sense of Normals

A Preliminary Report

WILLIAM K. BOARDMAN, Ph.D.; SANFORD GOLDSTONE, Ph.D., and WILLIAM T. LHAMON, M.D.,
Houston, Texas

Introduction

Much of the interest in lysergic acid diethylamide (LSD) is due to its capacity to produce schizophrenic-like behavior when administered in extremely small quantities.[4,6] Among the reported changes resulting from LSD have been alterations in time perception. DeShon, Rinkel, and Solomon,[1] found changes in the form of experiences of acceleration, retardation, or nonexistence of time, while "true disorientation" was not observed. The subjects of Hoch, Cattell, and Pennes [3] reported the passage of time as slowed, an experience not uncommon to schizophrenic patients.

An objective study of the time sense of schizophrenics [5] indicated that this population overestimates short audible durations to a significantly greater degree than do normal controls. The purpose of the present investigation was to determine whether moderate to low doses of LSD produce alterations in the time sense of normal subjects in the direction characteristic of schizophrenia, using the same method as reported previously.

Method

Procedure I.—Subjects consisted of four men, ranging in age from 30 to 35 years.

Submitted for publication March 6, 1957.

From the M. D. Anderson Department of Psychiatry, Baylor University College of Medicine, Texas Medical Center.

Supported in part by a grant (M-1121) from the National Institute of Mental Health, U. S. Public Health Service, and by the U. S. Air Force under Contract AF 18(603)-79, monitored by the Office of Scientific Research of the Air Research and Development Command.

An electronic timer was used to activate an audio-oscillator that delivered through headphones a tone of approximately 700 cps for durations between 0.01 and 9.99 seconds at 0.1-second step intervals. Subjects reported whether each tone heard was more or less than one second. Twenty runs, starting at 1.0 second and changing by 0.1-second intervals, were presented initially. If "more" was reported to the 1.0-second stimulus, the first run descended by 0.1-second step intervals and terminated when the subject reported "less" to three consecutive durations. The subsequent run began 0.1 second below the shortest stimulus of the descending run and increased by 0.1-second steps until the subject reported "more" to three consecutive presentations. Another descending run was then initiated, beginning 0.1 second above the longest stimulus of the ascending run. If the response to the initial 1.0-second stimulus was "less," the first run was ascending. The first 10 of the 20 runs represented a period of stabilization and were not included in the statistical calculations. Subsequent testings on the same day also started at 1.0 second but employed only 10 runs.

The percentages of reports of "less" for all durations were plotted on normal probability paper and a straight line visually fitted. The duration at which the subject would report "more" and "less" each 50% of the time was derived, as was the standard deviation of the subject's judgments. The 50% point was designated the subject's second estimation point (SEP), or that duration which the subject at the time of the test believed to be one second of clock time. The subject's coefficient of variation (*C*) was determined by dividing his standard deviation by his SEP.

LSD was administered to three subjects in the proportion of 0.75γ per kilogram of body weight. The fourth subject received a dose of 20γ.

On the test day, the subject was studied before drug administration and at regular intervals thereafter until the clinically observable peak effects had subsided.

Procedure II.—Subject 4 was subsequently tested on five different days in a double-blind study

in which small doses of LSD and a distilled-water placebo were used. Previously Subject 4 had been tested on numerous occasions, and his SEP was found to be very stable under standard conditions.

A method of constant stimuli was used, employing a series of six fixed durations of from 0.63 to 1.00 second at 10%-step intervals. The subject's SEP, as previously determined, approximated the mid-value of this stimulus series.

The stimuli were systematically randomized. The subject's SEP and *C* values were determined by a least squares solution.[3] The graphic method was not used to avoid the scoring bias in the visually fitted straight line. The subject was tested at frequent intervals for at least five hours after drug ingestion. One day of testing with no drug was carried out to provide additional control measures.

Results

All subjects in the initial study evidenced clinical effects usually associated with the dose levels used. Table 1 gives the LSD dosage, SEP's and *C* values under Procedure 1. The SEP's obtained after administration of LSD fluctuated but did not show an alteration in the direction of those reported for schizophrenics; i. e., they did not become smaller.

Three subjects showed a postdrug *C* increase of more than 45%. This change occurred in conjunction with reports by the subjects that they experienced extreme difficulty in maintaining a frame of reference on which to base their judgments of duration. Subject 3 had a high predrug coefficient of variation and did not follow the pattern of the others with respect to variability changes. It may be of interest to note that this subject had an initial SEP considerably smaller than that of the other tested subjects.

TABLE 1.—*Dosage, Second Estimation Points (SEP's) and Coefficients of Variation Obtained with Predrug and Postdrug Tests in Procedure 1*

	Minutes Postdrug					
Subject 1						
(55 γ)		0	90	180		
SEP		1.62	1.47	1.53		
C		9.8	19.0	10.5		
Subject 2						
(56 γ)		0	120	180		
SEP		1.42	1.86	1.53		
C		9.2	13.4	8.5		
Subject 3						
(52 γ)		0	120	210		
SEP		0.40	0.52	0.69		
C		20.0	11.5	23.2		
Subject 4						
(20 γ)	0	75	105	125	240	390
SEP	0.62	0.71	0.70	0.60	0.62	0.60
C	7.9	2.8	2.9	11.7	16.1	3.3

The SEP remained stable throughout the double blind experiment. This finding is consistent with that obtained with the larger dose levels of LSD: The time sense was not altered in the direction of that of the schizophrenic.

Coefficients of variation for all tests of the double-blind study are presented in Table 2. The values obtained under the placebo and no-drug conditions varied between 4.5% and 9.7%. With the various doses of LSD values of 15.8% or greater were obtained. *C* values under LSD conditions (mean value 10.27%) were compared with those under placebo and no-drug conditions (mean value 6.73%) by a *t*-test and were found to be significant at the 0.005 level. While LSD in moderate or small doses did not significantly

TABLE 2.—*Dosage, Times Tested, and Coefficients of Variation of Subject 4 for Each Day of Double-Blind Study*

Date: 10/17/56 Dose: 7 γ Time: 10:20 A.M.		10/22/56 No drug		11/2/56 12 γ 10:10 A.M.		11/23/56 4 γ 11:15 A.M.		11/30/56 Placebo 11:40 A.M.	
Time	*C* Value	Time	*C* Value	Time	*C* Value	Time	*C* Value	Time	*C* Value
9:45	5.9	9:10	8.6	10:00	6.3	11:10	8.2	11:30	9.0
10:35	9.4	10:35	9.7	10:26	8.5	11:31	8.8	12:19	8.8
11:30	15.8	11:20	5.3	10:55	5.0	12:10	15.7	12:50	4.5
11:55	14.6	11:55	5.0	11:18	7.5	1:11	16.8	1:20	6.3
12:47	12.5	12:47	7.5	11:40	4.7	1:46	7.0	2:17	9.0
2:00	14.9	2:15	8.4	12:50	8.4	2:36	6.1	3:10	7.0
3:00	9.9	3:00	5.2	1:50	9.3	3:06	7.2	3:48	6.1
5:50	12.7	4:00	5.2	2:00	7.4	3:23	9.7	4:50	6.5
				2:20	6.1	3:48	8.4		
				3:00	17.2	4:30	11.6		
				3:22	7.0	5:00	11.6		
				4:00	18.3	5:35	10.4		

alter the SEP of normals, amounts as small as 4γ increased the variability of one subject's judgments of short durations with the method used.

Comment

While the number of subjects and the dosages used limit the conclusions which may be drawn from the above findings, the consistency of the test responses produced by LSD in all four subjects suggests that stable temporal concepts and increased variability may be typical of the effects of this drug. The subjects who received LSD reported subjective effects, emphasizing the inability to maintain their concept of a second. If LSD in the amounts administered acted to produce a schizophrenic-like overestimation of time, this should have been reflected in decreased SEP's. Schizophrenic subjects did not demonstrate an increased coefficient of variation along with their shortened SEP; LSD subjects did not demonstrate a shortened SEP along with their increased coefficient of variation.

If the short SEP of the schizophrenic is considered to represent a shifted frame of reference resulting in a quantitatively different perception of time, LSD appears to produce a different effect in the normal. The increased coefficient of variation obtained with LSD and the difficulty in making a judgment, both occurring without a significant shift in SEP, indicate that the frame of reference used in making temporal judgment has not shifted but has become vague, and at times unavailable. The schizophrenic reports his thoughts are racing while on the outside time stands still; the normal with LSD is unable to say what the period of time between two events was or to estimate with any certainty or consistency the duration of a particular occurrence.

This failure to make accurate judgments of temporal durations does not produce "disorientation," since the subject remembers the hour, day, month, etc. The findings of other authors that subjects' perception of time is slowed or accelerated by LSD may be based on subjective reports that a single period of time seemed much longer or shorter than its clock duration. In view of the present results, the judgment of a single duration would not provide sufficient evidence of an altered time perception, since it might represent increased variability rather than consistently altered judgments.

If normal subject's LSD symptoms represent responses to a relative loss of frames of reference, while the schizophrenic subject has a definite, but invalid, frame of reference, a qualitative difference between LSD psychosis and schizophrenia is suggested. Increased judgment variability might be more appropriately related to anxious states or toxicity-determined thinking, while altered frame of reference might be characteristic of schizophrenia.

The dramatic variability changes with very low doses of LSD suggest that minute quantities of this drug may have measurable effects on aspects of behavior. Additional investigation is needed to confirm the responsivity of other subjects to low doses, and to examine the relationship between initial SEP and reaction to LSD and the correlation of increased variability with other behavior.

The present method of measurement appears to be unusually sensitive to the effects of LSD and should prove valuable as a standard against which to compare other types of assessment of the action of this drug.

Summary

The estimation of one second was studied in four men before and after administration of LSD. A schizophrenia-like increase in overestimation of short durations was not found, but the coefficient of variation of three subjects increased, suggesting that temporal frames of reference tended to become vague or "lost." A double-blind study of one subject with low doses of LSD and a distilled-water placebo gave similar results: no shift in temporal concept after LSD but an increase in variability of judgment with doses as small as 4γ. Some implications of

the differences between the measures obtained with schizophrenics and with normals given LSD are discussed. Further applications of the method are suggested.

M. D. Anderson Department of Psychiatry, Baylor University College of Medicine.

REFERENCES

1. DeShon, H. J.; Rinkel, M., and Solomon, H. C.: Mental Changes Experimentally Produced by LSD (d-Lysergic Acid Diethylamide Tartrate), Psychiat. quart. 26:33, 1952.

2. Guilford, J. P.: Psychometric Methods, Ed. 2, New York, McGraw-Hill Book Company, Inc., 1954.

3. Hoch, P. H.; Cattell, J. P., and Pennes, H. H.: Effects of Mescaline and Lysergic Acid (d-LSD-25), Am. J. Psychiat. 108:579, 1952.

4. Hoch, P. H.: Experimental Psychiatry, Comments, Am. J. Psychiat. 111:787, 1955.

5. Lhamon, W. T., and Goldstone, S.: The Time Sense: Estimation of One Second Durations by Schizophrenic Patients, A. M. A. Arch. Neurol. & Psychiat. 76:625, 1956.

6. Rinkel, M.; DeShon, H. J.; Hyde, R. W., and Solomon, H. C.: Experimental Schizophrenia-like Symptoms, Am. J. Psychiat. 108:572, 1952.

Books

Dance in Psychotherapy. By Elizabeth Rosen. Price, $4.50. Pp. 178. Columbia University Press, 2960 Broadway, New York 27, 1957.

In recent years more and more emphasis has been placed upon the broader experiences of the hospitalized psychiatric patient and the specific uses of these experiences as therapeutic for him. Many "therapies" have mushroomed in this fertile field of activities, and attempts are being made to specialize and separate out their unique contributions for psychiatric treatment, be it a specializing of psychotherapeutic approaches or an establishing of areas in milieu therapy programs. Though recognition has been given to these activities and their application is noted in hospitals throughout the country, investigative work comparable to the degree of their acceptance has not been published to evaluate and justify their use.

Miss Rosen has attempted to do this with regard to dance by reviewing its past application and describing her own planned, investigative programs. The first section of her book deals with a description of her proposed study, its working hypotheses and procedures. The contents of the book are then outlined.

Recreation and the creative arts are described in a basic, instructive manner in the next section. The method of prescribing activity so as to meet the patient's therapeutic needs, the philosophy of activity for the hospitalized patient, and specific application of activities, as well as possible variations of activities themselves, are reviewed. Miss Rosen has used many references and direct quotations for her review of these "adjunctive services" which serve to strengthen the authors' descriptions and clearly illustrate the bias of those quoted.

Miss Rosen then describes the history, philosophy, and practice of the dance. She uses the words of those who understand dance and those who understand human behavior. She combines the two for a relatively accurate description of the dance in today's society and its possible meaning for the psychotic patient.

The remainder of the book is considered by the reviewer to be the most pertinent and interesting. It consists of the description of three experimental dance programs. Rather minute, detailed description is included of the hospitals in which the programs took place. Though repetitive and full of statistics, the reader is given a clear picture of the environment in which the patients live and the dance programs took place. Miss Rosen's method of study is, first, to relate the behavior of the patients in the dance group and, second, to study the individual patient's application of the dance experience. The patients' comments, both written and verbal, of their experiences during the dance programs are used well by the author to illustrate her therapeutic aims.

The book as a whole is written in a basic, elementary fashion, which a beginning student would find helpful. For persons experienced in hospital milieu therapy the beginning chapters may become tedious. For the facetious, the title "Dance in Psychotherapy" may suggest the comment "Let's," but the chapters containing the description of the dance classes, the problems found, and how they were solved are well worth the reading. The introductory material is pertinent but could be gotten by reading the author's own summary at the close of each of these chapters.

Pointed out by the clinical material of the book is the need for more understanding of group techniques by those who by virtue of their skills will be working mainly with individuals in a group setting. The author sums up the problem when she concludes the book with the comment that the "future of dance therapy . . . will depend in part upon the ability of its instigators and leaders to share their experiences with each other" and "make available their clinical experiences," which Miss Rosen has done.

"There are dances of birth, of death, of war, of fertility, of harvest, and for religious functions," says Dr. Bela Mittelmann, eminent psychiatrist, in his foreword to Elizabeth Rosen's new book "Dance in Psychotherapy." Because dance can be used to express human needs and emotions nonverbally, and sometimes even unconsciously, it has recently been seen as a promising auxiliary therapy in the treatment of the mentally ill.

"Dance in Psychotherapy" is an absorbing account of a pioneering attempt to explore this promise. About her study Dr. Rosen says: "The initial goal of all methods of therapy

with the schizophrenic patient is to establish contact. In my book I have tried to describe how dance was used—and can be used by others—as an opening wedge in developing social responsiveness in the patient."

Two chapters of the book are devoted to detailed descriptions of two experimental dance projects—one at Hillside Hospital, on Long Island, the other at Manhattan State Hospital, in New York City. Dr. Rosen tells how the programs were planned and what actually occurred in the dance sessions, describes methods and materials used, and reports the patients' reactions to the dance itself, to the leader, and to each other as a group. Pictures of actual dance sessions show the kinds of activities engaged in. Also included are detailed individual case reports, carefully interpreted.

The author also gives an excellent historical account of the use of recreation and art in the treatment of mental patients and outlines the rationale on which such programs are based. Dance is then discussed in relation to these auxiliary therapies, and its unique aims and techniques are pointed out.

From Custodial to Therapeutic Patient Care in Mental Hospitals: Explorations in Social Treatment. By Milton Greenblatt, Richard H. York, and Esther Lucile Brown, in collaboration with Robert W. Hyde. Price $5.00. Pp. vii + 497. Russell Sage Foundation, 505 Park Ave., New York 22, 1955.

Recently a large number of American psychiatric hospitals have undergone reorganization, and many have made great progress in the transition toward the creation of a "therapeutic" atmosphere. These changes have been facilitated by increased allocation of funds, qualitative and quantitative improvement in personnel, and enthusiasm regarding the therapeutic potentialities of psychotherapy, group therapy, tranquilizing drugs, and sociotherapy. The authors have done an excellent job in describing the current spirit of renewed optimism and humanism in hospital psychiatry. Primarily, however, their enthusiasm is limited to the treatment possibilities inherent in altering the social environment of the psychiatric hospital. They have graphically described stages in the evolution of the social structure of three hospitals in the Boston area—the Boston Psychopathic Hospital; Veterans' Administration Hospital, Bedford, Mass., and the Metropolitan State Hospital, Waltham, Mass. Formerly each of these institutions was predominantly a custodial center, geared toward encapsulating frequently occurring emergency situations. Since the patients were largely viewed as unpredictable, dangerous, and irrational, they were not included in the day-to-day hospital planning, and, in addition, rigid hierarchical lines prevailed within the staff organization. At differential rates of speed all three hospitals changed their total philosophy (actually an attempt was made to apply methods of patient care learned at the Boston Psychopathic Hospital to the other two hospitals), with resultant widespread patient and staff participation in decision-making processes. Admission procedures, recreational activities, staff meetings, and almost every aspect of the hospital setting were reorganized along the lines of communicating mutual respect between patient and staff groups in everyday actions and procedures. Remarkable changes ensued, with decreased necessity for patient seclusion and restraint, while hospital crises became infrequent. The authors record these developments in clear tables and figures, which lend authority to their statements.

The book has many interesting features for students of social psychiatry as applied to the hospital setting. The bibliography is exceptionally good, with excellent organization and a complete listing of the entire relevant material. Administrators will be interested in the leadership practices which proved so effective in these hospitals. Changing role concepts of nurses, attendants, occupational therapists, and recreational personnel are clearly defined in a manner that should be quite useful for these groups. Researchers who study the psychiatric hospital as a system, with multiple subparts in transaction with each other, will find a large amount of interesting data, as well as suggestions for future research direction. The reviewer was especially impressed with the research potentiality of comparing three hospitals in varying transitional states of change in social structure.

Several factors, however, limit the acceptance of a cause-and-effect relationship between the reported changes in social environment and the patient improvement. The major problem lies in the rapid rate of change in hospital operational practices, as compared with the relatively poor status of theory in social psychiatry in both the specific hospital context and the general field. When the major assumptions underlying this book are crystallized, what

emerges is a belief in the egalitarian ideal, a respect for democratic practices and wide participation in decision making, and the hope that open channels of communication reduce intrahospital tension. When the above are coupled with good leadership and changes in staff-patient interactions, so that mutual respect replaces mutual fear, patients seem to improve, and the staff feels much more comfortable. What remains unanswered at present is how and why patients improved under these conditions. These questions cannot be answered until much more research work is done in the attempt to integrate the intraindividual and intra-hospital systems. It is quite possible that much of the patients' improvement recorded in this book may be due to staff enthusiasm about changes in the social structure of the hospital rather than be a resultant of the actual changes. Will the improvement last when a plateau is reached in the rate of change and enthusiasm wanes? This, of course, remains to be seen, but the question must be raised for purported therapeutic changes in social environment, just as it has been raised in discussing changes attributed to tranquilizing drugs and other forms of therapy. Enthusiastic identification with a specific form of therapy tends to block out other relevant factors operating in the field. As an example, in this book the authors tend to speak more positively of changes induced by lobotomy (page 102) than might have been anticipated from their main theme. It seems that they shift at this point from a predominantly sociotherapeutic orientation to a somatotherapeutic philosophy without integrating these theoretical models, and this seems to be a reflection of the fact that lobotomy studies were carried out concomitantly with the social changes at the Boston Psychopathic Hospital. Decades of theoretical conceptualization and experimental studies involving the hospital system remain to be accomplished before authoritative statements regarding the relationship of social environmental changes to therapeutic results can be made.

With the above limitations in mind, the value of the book can be seen in a better perspective. It serves as an excellent description of changes that almost all personnel working in psychiatric hospitals believe to be worth while. Hopefully, future psychiatrists will view this book as an important milestone, describing initial stages in the transition toward hospitals proved to be therapeutic by experimental validation.

La Psychanalyse d'aujourd'hui. Two Volumes. Edited by S. Nacht. Price, not given. Presses universitaires de France, 108 boulevard Saint-Germain, Paris, 1956.

This important summary of the present status of psychoanalysis originates from the Institute for Psychoanalysis of Paris, founded in 1953. Its purpose is stated to be "to transmit and continue the work of Freud." It consists of a series of essays by twenty-four different authors on various phases of psychoanalysis and its relation to education, medicine, neurobiology, and mental prophylaxis; its relationships to literature and linguistics are not discussed.

As might be expected in a work of multiple authors, the chapters are not all equally good; some are largely collections of case histories, and others are careful and critical discussions. The authors range from Marie Bonaparte, who initiated the study of psychoanalysis in France, and S. Nacht, the director of the Institute, to others who are less well known. The best chapters are written by Nacht, who gives every indication of attempting to be candid and objective. These chapters could well be read with profit by anyone entering into the study of psychoanalysis.

As might be expected, every effort is made to present psychoanalysis in the best light possible. No attempt is made to relate it to the classical French tradition, although several authors state that such a synthesis must be made. The ghost of Janet floats through the pages, although rarely recognized. In fact, the first impression one gets in reading the work is how alien it all is to the French tradition. This is not astonishing, since it deals with an alien development and a large proportion of the authors are not French.

The work is also marred by the inability of many authors to stick to their subject. As is characteristic of psychoanalytic writing in general, fact and fancy are intermingled, and one finds a prevalent fear of being unorthodox; hence a constant attempt to prove that they are really not betraying the thought of Freud. Nevertheless, evidences of unorthodox trends abound. It is clear that the analysts in France tend to place less emphasis on the uncovering of traumatic memories and experiences and more on the emotional impact of the analyst on the patient. It is evident also that the less consensus exists concerning a given topic, the longer the chapter tends to be. There is also a good deal of repetition, since most of the authors cannot resist the temptation to launch out into theorizing, which is repeated in other words in other chapters.

M. Bouvet makes the interesting observation that Oedipal neuroses (phobias and hysterias according to him) are less and less frequently encountered in France, an observation which, if true, is fraught with important implications. M. Held notes that, in France, it is difficult to get the medical student to forget his Cartesian formation. There is much complaining of the resistance of the internists in the hospitals, to which the analysts have been admitted, to their dynamic formulations. When one remembers what stubborn resistance was offered to the teachings of Lister and of Semmelweis, one wonders why analysts should expect their colleagues to accept their teaching without demonstration of its value in actual experience. Have they never been taught medical history? It is perhaps significant that one author remarks, "Nothing, or at least nothing valuable, preceded or prepared the essential discoveries of Freudian psychology." In many places in these essays it is evident that the French analysts are still hypersensitive, giving evidence of a deep-seated feeling of insecurity. It is true that there are scoffers in France, as elsewhere, but the analysts were admitted to the psychiatric clinic of the University of Paris by Professor Claude, on the same basis as other psychiatrists, as long ago as 1925.

There is no attempt to present psychoanalysis as a cure-all. The essays abound in warnings and cautions. It is said to be of largely "Platonic" interest in the treatment of psychoses, of no use in homosexuals, of limited usefulness in severe phobias and obsessions, of use in children only when its procedures are altered so as to be called psychoanalytic only by courtesy, and of limited usefulness in adolescents unless accompanied by intensive active reeducation. Even in those cases in which the method gives best results, in hysteria and simple phobias of young adults under 40, the physician is warned that relapses are frequent. The difficulties and dangers of the treatment, especially in adolescence, are elaborately discussed.

Schlumberger and Marty give a useful history of the historical development of psychoanalysis in France. It is interesting to note that it was introduced by Marie Bonaparte and Eugenie Sokolnicka, neither a physician, but that S. Nacht, the present director of the Institute, gives many reasons why an analyst should be a physician.

In spite of the interminable theorizing and considerable redundancy, the reader will find these essays give a very illuminating picture of the state of psychoanalysis in France, if he has the patience to wade through them, and a few of them, especially those by S. Nacht, will be found richly rewarding.

when your patients need to be

stimulated

not tranquilized

You will find that 'Dexedrine'—a standard antidepressant—helps dispel apathy and lethargy, restoring optimism, energy and a sense of well-being in your depressed patients. 'Dexedrine' is available as tablets, elixir, and Spansule† sustained release capsules.

Smith, Kline & French Laboratories, Philadelphia

Dexedrine*

*T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.
†T.M. Reg. U.S. Pat. Off.

HALL-BROOKE

An Active Treatment Hospital

A licensed private hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

A high ratio of staff to patients.

Large occupational therapy building with a trained staff offers complete facilities for crafts, arts and recreation. Full program of outdoor activities.

Each patient is under constant, daily psychiatric and medical supervision.

Located one hour from New York on 120 acres of Connecticut countryside.

HALL-BROOKE

Greens Farms, Box 31, Conn., Tel.: Westport, CApital 7-5105

George S. Hughes, M.D.
Leo H. Berman, M.D.
Alfred Berl, M.D.
Louis J. Micheels, M.D.
Robert Isenman, M.D.
John D. Marshall, Jr., M.D.
Peter B. Barbara, Ph.D.
Mrs. Heide F. Bernard and Samuel Bernard, Administrators

NEW YORK OFFICE, 46 East 73 Street
Telephone: Lehigh 5-5155

ADAMS HOUSE

Established 1877

☆

A non-commitment sanitarium and clinic, club-like in physical setting and atmosphere, applying re-educational psychotherapeutic methods in the study and treatment of the **psychoneuroses** exclusively.

Located in suburban Boston contiguous to and overlooking the Arnold Arboretum

☆

James Martin Woodall, M.D., Medical Director

990 CENTRE STREET, BOSTON,
Jamaica Plain, MASS.

BALDPATE, Inc.

Georgetown, Mass.

Geo. Fleetwood 2-2131

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Definitive psychotherapy, somatic therapies, pharmacotherapy, milieu-therapy under direction of trained occupational and recreational therapists.

HARRY C. SOLOMON, M.D. — *Consulting Psychiatrist*
GEORGE M. SCHLOMER, M.D. — *Medical Director*

Appalachian Hall

Established 1916
Asheville, North Carolina

An Institution for the diagnosis and treatment of Psychiatric and Neurological illnesses, rest, convalescence, drug and alcohol habituation.
Insulin Coma, Electroshock and Psychotherapy are employed. The Institution is equipped with complete laboratory facilities including electroencephalography and X-ray.
Appalachian Hall is located in Asheville, North Carolina, a resort town, which justly claims an all around climate for health and comfort. There are ample facilities for classification of patients.

WM. RAY GRIFFIN, JR., M.D. — MARK A. GRIFFIN, SR., M.D.
ROBERT A. GRIFFIN, M.D. — MARK A. GRIFFIN, JR., M.D.

For further information write APPALACHIAN HALL, ASHEVILLE, N. C.

RIVER CREST SANITARIUM

FOR

NERVOUS, MENTAL, AND ALCOHOLIC PATIENTS

Layman R. Harrison, M.D.
Physician in Charge

Martin Dollin, M.D.
Clinical Director

Russell N. Carrier, M.D.
Consultant in Psychotherapy

Arthur Gordon, M.D.
Consultant in Medicine

Katherine C. Kindred
Administrator

Approved for resident training in Psychiatry

A private hospital for the care and treatment of nervous and mental disorders. All accepted types of treatment available. Individualized attention to psychotherapy, insulin and electroshock therapy.
A cottage maintained expressly for elderly women with problems of senility and continued care. We also have accommodations for men requiring continued care.
River Crest is located in a beautifully wooded and landscaped park of about twelve acres, secluded but easily accessible by subway, bus or private car.
Full cooperation with referring physicians, who will find it convenient to visit or participate in the treatment of their patients while at River Crest.

Ditmars Boulevard and 26th Street
ASTORIA, L. I., NEW YORK CITY
AS 8-0820
TWENTY MINUTES FROM TIMES SQUARE

FAIRVIEW Sanitarium

2828 S. PRAIRIE AVE.
CHICAGO
Phone VIctory 2-1650
J. DENNIS FREUND, M.D.
Medical Director

DEVOTED TO THE ACTIVE TREATMENT OF

MENTAL and NERVOUS DISORDERS

Specializing in Psycho-Therapy, and Physiological therapies including:

- Insulin Shock
- Electro-Narcosis
- Electro-Shock
- Out Patient Shock Therapy Available

ALCOHOLISM Treated by Comprehensive Medical-Psychiatric Methods.

"Beverly Farm"

INCORPORATED
Founded 1897
INCORPORATED 1922

12 buildings
220 acres of land
300 feet above
Mississippi River

HOME AND SCHOOL FOR
Nervous and Backward Children

Can accommodate 350 children, with contemplated educational improvements for a larger number. Can accept some suitable case for life.

Address all communications to DR. GROVES B. SMITH, SUPERINTENDENT
"Beverly Farm" GODFREY, MADISON COUNTY, ILLINOIS

MARY POGUE SCHOOL, Inc.

Complete facilities for training, educationally and socially, the retarded and epileptic. Girls from 8 and boys from 4—separate living accommodations. Small classes. Individual assistance. Physical and occupational therapy and recreational programs. Long term residential care available. Institutional member I.H.A. and A.H.A.
Catalogue on request.

G. H. Marquardt, M.D. *Medical Director*
Barclay J. MacGregor *Registrar*

65 Geneva Road, Wheaton, Ill. (near Chicago)

RING SANATORIUM

Eight Miles from Boston—Founded 1879

For the study, care, and treatment of emotional, mental, personality, and habit disorders.
On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.
Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.
Full resident and associate staff. Courtesy privileges to qualified physicians.

BENJAMIN SIMON, M.D.
Director
CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts
MIssion 8-0081

YOUR
GUIDE TO
CURRENT PUBLICATIONS

Quarterly Cumulative Index Medicus

WITH AUTHORS AND SUBJECTS . . .

Divided into sections, one devoted to books and the other to periodical literature, the QUARTERLY CUMULATIVE INDEX MEDICUS contains a list of current publications alphabetized as to authors and subjects. The exact bibliographic reference is given under the author with titles in the original language, while titles under subjects are all in English. The index also includes a listing of journals, addresses and publishers.

The QUARTERLY CUMULATIVE INDEX MEDICUS appears twice a year; volumes are cloth bound and cover periodicals for six months as indicated on the publication. These two volumes will be a convenient and inclusive reference for current medical literature. Invaluable for practitioners, specialists, teachers, editors, writers, investigators, students and libraries.

SUBSCRIPTION PRICE $25.00 PER YEAR
CANADIAN AND FOREIGN $27.00 PER YEAR

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

All of these articles have appeared in TODAY'S HEALTH and are now available in one pamphlet.

ALCOHOLISM

an important problem in today's living

ALCOHOLICS ANONYMOUS

Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.

ALCOHOL AND CIRRHOSIS OF THE LIVER

Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences.
by Russell S. Boles

HOW TO HELP A PROBLEM DRINKER

Understanding the alcoholic's capabilities, the necessity of help, causes of his condition.
by Edward A. Strecker and Francis T. Chambers, Jr.

THE TREATMENT OF ALCOHOLISM

Tracing the steps from convincing the alcoholic that he is sick through treatment and cure.
by Lewis Inman Sharp

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM

Its place among methods of treatment today, its development and correlation with personality factors.
by Walter L. Voegtlin

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM

Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel.
by E. H. L. Corwin

THE ABOVE SIX PAMPHLETS ARE AVAILABLE IN BOOKLET FORM FOR ONLY 50 CENTS

HOW EXPERTS MEASURE DRUNKENNESS

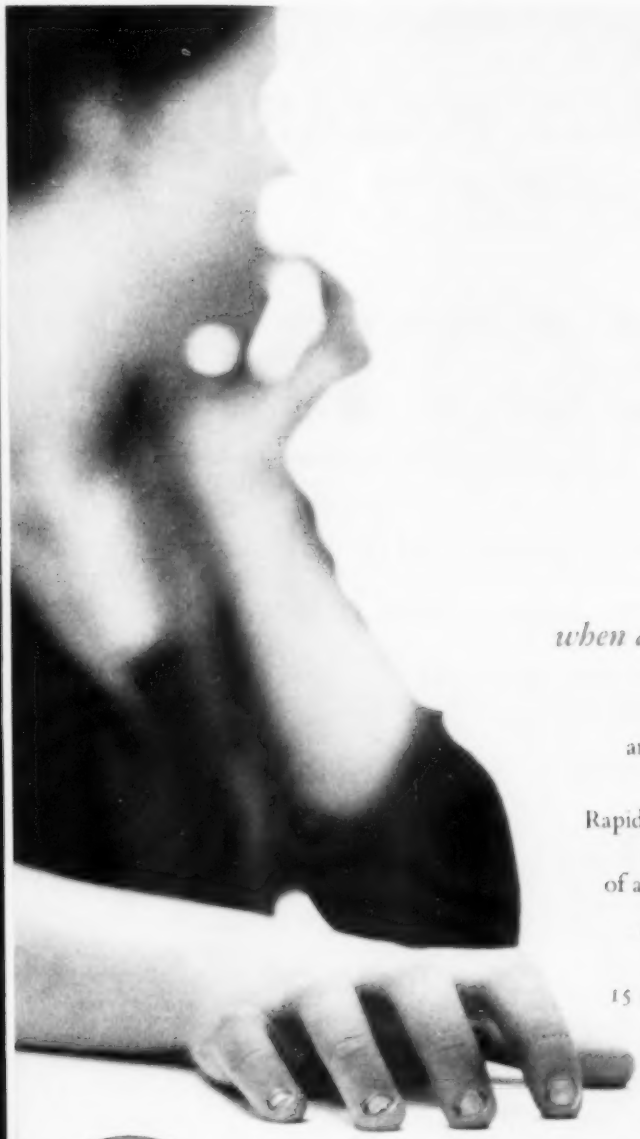
A partial transcript of an actual courtroom case.
H. A. Heise
8 pages, 15 cents

BARBITURATES, BOOZE AND OBITUARIES

A discussion of the dangers of mixing alcohol and barbiturates.
Donald A. Dukelow
4 pages, 10 cents

ADDRESS REQUESTS TO:

ORDER DEPARTMENT
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS



when anxiety is the diagnosis,

or when anxiety aggravates
an existing disorder, 'Compazine'
is remarkably effective.

Rapidly and with minimal side effects,
'Compazine' relieves most cases
of anxiety, nervousness and tension.

Available:

Spansule† capsules, 10 mg. and
15 mg.; tablets, 5 mg., 10 mg. and,
primarily for use in psychiatry,
25 mg.; ampuls, 10 mg. (2 cc.)

Compazine★

to tranquilize with remarkable freedom from drowsiness and depressing effect

Smith, Kline & French Laboratories, Philadelphia

★T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F. Patent Applied For

MINIMIZE HAZARDS of E.C.T.

'ANECTINE'®

Chloride brand Succinylcholine Chloride

"...removes practically all the previous risks inherent in the treatment."[16]

Confirming the contribution of 'Anectine' to safe E.C.T. therapy:

1. **Brody, J. I.** and **Bellet, S.**: Am.J.M.Sc. **233**:40 (Jan.) 1957.
2. **Impastato, D. J.** and **Gabriel, A. R.**: Dis.Nerv.System **18**:334 (Jan.) 1957.
3. **Impastato, D. J.** and **Berg, S.**: Am.J.Psychiat. **112**:893 (May) 1956.
4. **Buckley, R. W.** and **Richards, W. L.**: Ohio State M.J. **52**:481 (May) 1956.
5. **Lewis, W. H., Jr.**: Dis.Nerv.System **17**:81 (Mar.) 1956.
6. **Moore, D. C.** and **Bridenbaugh, L. D., Jr.**: Anesthesiology **17**:212 (Jan.) 1956.
7. **Jacoby, J.**, *et al.*: J.Clin.& Exper.Psychopathol. **16**:265 (Dec.) 1955.
8. **Newbury, C. L.** and **Etter, L. E.**: A.M.A.Arch.Neurol.& Psychiat. **74**:472 (Nov.) 1955.
9. **Newbury, C. L.** and **Etter, L. E.**: *Ibid.* **74**:479 (Nov.) 1955.
10. **Impastato, D. J.**: J.M.Soc.New Jersey **52**:528 (Oct.) 1955.
11. **Lincoln, J. R.** and **Broggi, F. S.**: New England J.Med. **253**:546 (Sept.) 1955.
12. **Tucker, W. I., Fleming, R.,** and **Raeder, O.**: *Ibid.* **253**:451 (Sept.) 1955.
13. **Rietman, H. J.** and **Delgado, E.**: Dis.Nerv.System **16**:237 (Aug.) 1955.
14. **Lewis, W. H., Richardson, D. J.,** and **Gahagan, L. H.**: New England J.Med. **252**:1016 (June) 1955.
15. **Glover, B. H.** and **Roisum, B. H.**: J.Nerv.& Ment.Dis. **120**:358 (Nov.-Dec.) 1954.
16. **Saltzman, C., Konikov, W.,** and **Relyea, R. P.**: Dis.Nerv.System **16**:153 (May) 1955.
17. **Robie, T. R.**: J.M.Soc.New Jersey **52**:82 (Feb.) 1955.
18. **Schiele, B. C.** and **Margolis, P. M.**: Minnesota Med. **38**:1 (Jan.) 1955.
19. **Wilson, W. P.**, *et al.*: A.M.A.Arch.Neurol.& Psychiat. **72**:550 (Nov.) 1954.
20. **Steven, R. J. M.**, *et al.*: Anesthesiology **15**:623 (Nov.) 1954.
21. **Holt, W. L., Jr.**: New York State J.Med. **54**:1918 (July) 1954.
22. **Holmberg, G.**, *et al.*: A.M.A.Arch.Neurol.& Psychiat. **72**:73 (July) 1954.
23. **Dewald, P. A., Margolis, N. M.,** and **Weiner, H.**: J.A.M.A. **154**:981 (Mar.) 1954.
24. **Wilson, W. P.** and **Nowill, W. K.**: A.M.A.Arch.Neurol.& Psychiat. **71**:122 (Jan.) 1954.
25. **Moss, B. F., Jr., Thigpen, C. H.,** and **Robinson, W. P.**: Am.J.Psychiat. **109**:895 (June) 1953.
26. **Holt, W. L., Jr.**, *et al.*: Confinia neurol. **13**:313, 1953.
27. **Murray, N.**: Texas Rep.Biol.& Med. **11**:593, 1953.
28. **Murray, N.**: Confinia neurol. **13**:320, 1953.
29. **Alexander, L., Gilbert, I. E.,** and **White, S. E.**: *Ibid.* **13**:325, 1953.
30. **McDowell, D. H., Rahill, M. A.,** and **Tyndall, J. A.**: J.Irish M.A. **31**:240, 1952.
31. **Holmberg, G.** and **Thesleff, S.**: Am.J.Psychiat. **108**:842, 1952.
32. **Altschule, M. D.** and **Tillotson, K. J.**: New England J.Med. **238**:113 (Jan.) 1948.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

Typical case: "unmanageable" schizophrenic patient is hostile, untidy and inaccessible to therapy.

the "before-and-after" picture in mental wards continues to improve, case after case, with **Serpasil**® (reserpine CIBA)

With Serpasil, patient becomes calm, cooperative, amenable to interview . . . as have thousands in this new age of hope for the psychotic.

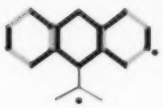
SUPPLIED:

Parenteral Solution:
Ampuls, 2 ml., 2.5 mg. Serpasil per ml.
Multiple-dose Vials, 10 ml., 2.5 mg. Serpasil per ml.

Tablets, 4 mg. (scored), 2 mg. (scored), 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg.

Elixirs, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

CIBA
SUMMIT, N. J.



withdrawn, apathetic patients

also can benefit from

THORAZINE*

'THORAZINE' CASE HISTORY

patient: 18-year-old female; "mute, incontinent, paid no attention to her personal appearance, and had to be fed."

results: "During the six weeks on ['Thorazine'], she became more friendly and talkative . . . ate normal meals and was no longer incontinent . . . facial expression and bearing were friendly and responsive."[1]

Smith, Kline & French Laboratories, Philadelphia

1. Shepherd, M., and Watt, D.C.: J. Neurol., Neurosurg. & Psychiat. *19*:232 (August) 1956.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.